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Zhu et al.

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(54) **HETEROCYCLIC ASPARTYL PROTEASE INHIBITORS**

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(Continued)

(52) **U.S. Cl.**
CPC ***C07D 233/88*** (2013.01); ***A61K 31/4168*** (2013.01); ***A61K 31/4178*** (2013.01); ***A61K 31/4184*** (2013.01); ***A61K 31/4439*** (2013.01); ***A61K 31/454*** (2013.01); ***A61K 31/4545*** (2013.01); ***A61K 31/4725*** (2013.01); ***A61K 31/5377*** (2013.01); ***A61K 31/655*** (2013.01); ***A61K 45/06*** (2013.01); ***C07D 233/46*** (2013.01); ***C07D 233/70*** (2013.01); ***C07D 235/02*** (2013.01); ***C07D 239/22*** (2013.01); ***C07D 239/70*** (2013.01); ***C07D 271/07*** (2013.01); ***C07D 273/00*** (2013.01); ***C07D 295/15*** (2013.01); ***C07D 401/04*** (2013.01); ***C07D 401/06*** (2013.01); ***C07D 401/08*** (2013.01);
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(58) **Field of Classification Search**
CPC C07D 265/02
See application file for complete search history.

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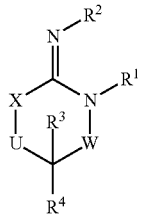
(57) **ABSTRACT**

Disclosed are compounds of the formula I

I



or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein

W is a bond, —C(=S)—, —S(O)—, —S(O)$_2$—, —C(=O)—, —O—, —C(R^6)(R^7)—, —N(R^5)— or —C(=N(R^5))—;

X is —O—, —N(R^5)— or —C(R^6)(R^7)—; provided that when X is —O—, U is not —O—, —S(O)—, —S(O)$_2$—, —C(=O)— or —C(=NR^5)—;

U is a bond, —S(O)—, —S(O)$_2$—, —C(O)—, —O—, —P(O)(OR^{15})—, —C(=NR^5)—, —(C(R^6)(R^7))$_b$— or —N(R^5)—; wherein b is 1 or 2; provided that when W is —S(O)—, —S(O)$_2$—, —O—, or —N(R^5)—, U is not —S(O)—, —S(O)$_2$—, —O—, or —N(R^5)—; provided that when X is —N(R^5)— and W is —S(O)—, —S(O)$_2$—, —O—, or —N(R^5)—, then U is not a bond;

and R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in the specification;

and pharmaceutical compositions comprising the compounds of formula I.

Also disclosed is the method of inhibiting aspartyl protease, and in particular, the methods of treating cardiovascular diseases, cognitive and neurodegenerative diseases, and the methods of inhibiting of Human Immunodeficiency Virus, plasmepins, cathepsin D and protozoal enzymes.

Also disclosed are methods of treating cognitive or neurodegenerative diseases using the compounds of formula I in combination with a cholinesterase inhibitor or a muscarinic antagonist.

10 Claims, No Drawings

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C07D 401/12	(2006.01)
C07D 403/04	(2006.01)
C07D 403/06	(2006.01)
C07D 403/08	(2006.01)
C07D 403/10	(2006.01)
C07D 403/12	(2006.01)
C07D 405/10	(2006.01)
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C07D 409/10	(2006.01)
C07D 409/14	(2006.01)
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C07D 413/12	(2006.01)
C07D 417/06	(2006.01)
A61K 31/4168	(2006.01)
A61K 31/4178	(2006.01)
A61K 31/4184	(2006.01)
A61K 31/4439	(2006.01)
A61K 31/454	(2006.01)
A61K 31/5377	(2006.01)
A61K 45/06	(2006.01)
C07D 295/15	(2006.01)
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C07D 409/06	(2006.01)
A61K 31/4545	(2006.01)
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A61K 31/655	(2006.01)
C07D 235/02	(2006.01)
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C07D 407/06	(2006.01)

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CPC ***C07D 401/10*** (2013.01); ***C07D 401/12*** (2013.01); ***C07D 401/14*** (2013.01); ***C07D 403/04*** (2013.01); ***C07D 403/06*** (2013.01); ***C07D 403/08*** (2013.01); ***C07D 403/10*** (2013.01); ***C07D 403/12*** (2013.01); ***C07D 405/06*** (2013.01); ***C07D 405/10*** (2013.01); ***C07D 405/14*** (2013.01); ***C07D 407/06*** (2013.01); ***C07D 409/04*** (2013.01); ***C07D 409/06*** (2013.01); ***C07D 409/10*** (2013.01); ***C07D 409/14*** (2013.01); ***C07D 413/10*** (2013.01); ***C07D 413/12*** (2013.01); ***C07D 417/06*** (2013.01)

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HETEROCYCLIC ASPARTYL PROTEASE INHIBITORS

This application claims the benefit of priority of U.S. Ser. No. 60/529,535, filed Dec. 15, 2003.

FIELD OF THE INVENTION

This invention relates to heterocyclic aspartyl protease inhibitors, pharmaceutical compositions comprising said compounds, their use in the treatment of cardiovascular diseases, cognitive and neurodegenerative diseases, and their use as inhibitors of the Human Immunodeficiency Virus, plasmepsins, cathepsin D and protozoal enzymes.

BACKGROUND

Eight human aspartic proteases of the A1 (pepsin-like) family are known to date: pepsin A and C, renin, BACE, BACE 2, Napsin A, cathepsin D in pathological conditions.

The role of renin-angiotensin system (RAS) in regulation of blood pressure and fluid electrolyte has been well established (Oparil, S, et al. N Engl J Med 1974; 291:381-401/446-57). The octapeptide Angiotensin-II, a potent vasoconstrictor and stimulator for release of adrenal aldosterone, was processed from the precursor decapeptide Angiotensin-I, which in turn was processed from angiotensinogen by the renin enzyme. Angiotensin-II was also found to play roles in vascular smooth muscle cell growth, inflammation, reactive oxygen species generation and thrombosis, influence atherogenesis and vascular damage. Clinically, the benefit of interruption of the generation of angiotensin-II through antagonism of conversion of angiotensin-I has been well known and there are a number of ACE inhibitor drugs on the market. The blockade of the earlier conversion of angiotensinogen to angiotensin-I, i.e. the inhibition of renin enzyme, is expected to have similar but not identical effects. Since renin is an aspartyl protease whose only natural substrate is angiotensinogen, it is believed that there would be less frequent adverse effect for controlling high blood pressure and related symptoms regulated by angiotensin-II through its inhibition.

Another protease, Cathespin-D, is involved in lysosomal biogenesis and protein targeting, and may also be involved in antigen processing and presentation of peptide fragments. It has been linked to numerous diseases including, Alzheimers, disease, connective tissue disease, muscular dystrophy and breast cancer.

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is ultimately fatal. Disease progression is associated with gradual loss of cognitive function related to memory, reasoning, orientation and judgment. Behavioral changes including confusion, depression and aggression also manifest as the disease progresses. The cognitive and behavioral dysfunction is believed to result from altered neuronal function and neuronal loss in the hippocampus and cerebral cortex. The currently available AD treatments are palliative, and while they ameliorate the cognitive and behavioral disorders, they do not prevent disease progression. Therefore there is an unmet medical need for AD treatments that halt disease progression.

Pathological hallmarks of AD are the deposition of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles comprised of abnormally phosphorylated protein tau. Individuals with AD exhibit characteristic Aβ deposits, in brain regions known to be important for memory and cognition. It is believed that Aβ is the fundamental causative agent of neuronal cell loss and dysfunction which is associated with cognitive and behavioral decline. Amyloid plaques consist predominantly of Aβ peptides comprised of 40-42 amino acid residues, which are derived from processing of amyloid precursor protein (APP). APP is processed by multiple distinct protease activities. Aβ peptides result from the cleavage of APP by β-secretase at the position corresponding to the N-terminus of Aβ, and at the C-terminus by γ-secretase activity. APP is also cleaved by α-secretase activity resulting in the secreted, non-amyloidogenic fragment known as soluble APP.

An aspartyl protease known as BACE-1 has been identified as the β-secretase activity responsible for cleavage of APP at the position corresponding to the N-terminus of Aβ peptides.

Accumulated biochemical and genetic evidence supports a central role of Aβ in the etiology of AD. For example, Aβ has been shown to be toxic to neuronal cells in vitro and when injected into rodent brains. Furthermore inherited forms of early-onset AD are known in which well-defined mutations of APP or the presenilins are present. These mutations enhance the production of Aβ and are considered causative of AD.

Since Aβ peptides are formed as a result β-secretase activity, inhibition of BACE-1 should inhibit formation of Aβ peptides. Thus inhibition of BACE-1 is a therapeutic approach to the treatment of AD and other cognitive and neurodegenerative diseases caused by Aβ plaque deposition.

Human immunodeficiency virus (HIV), is the causative agent of acquired immune deficiency syndrome (AIDS). It has been clinically demonstrated that compounds such as indinavir, ritonavir and saquinavir which are inhibitors of the HIV aspartyl protease result in lowering of viral load. As such, the compounds described herein would be expected to be useful for the treatment of AIDS. Traditionally, a major target for researchers has been HIV-1 protease, an aspartyl protease related to renin.

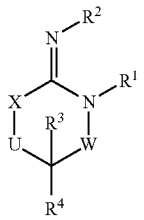
In addition, Human T-cell leukemia virus type I (HTLV-I) is a human retrovirus that has been clinically associated with adult T-cell leukemia and other chronic diseases. Like other retroviruses, HTLV-I requires an aspartyl protease to process viral precursor proteins, which produce mature virions. This makes the protease an attractive target for inhibitor design. Moore, et al. Purification of HTLV-I Protease and Synthesis of Inhibitors for the treatment of HTLV-I Infection 55^{th} Southeast Regional Meeting of the American Chemical Society, Atlanta, Ga., US Nov. 16-19, 2003 (2003), 1073. CODEN; 69EUCH Conference, AN 2004:137641 CAPLUS.

Plasmepsins are essential aspartyl protease enzymes of the malarial parasite. Compounds for the inhibition of aspartyl proteases plasmepsins, particularly I, II, IV and HAP, are in development for the treatment of malaria. Freire, et al. WO 2002074719. Na Byoung-Kuk, et al. Aspartic proteases of *Plasmodium vivax* are highly conserved in wild isolates Korean Journal of Prasitology (2004 June), 42(2) 61-6. Journal code: 9435800 Furthermore, compounds used to target aspartyl proteases plasmepsins (e.g. I, II, IV and HAP), have been used to kill malarial parasites, thus treating patients thus afflicted. Certain compounds also exhibited inhibitory activity against Cathespin D.

SUMMARY OF THE INVENTION

The present invention relates to compounds having the structural formula I

I



or a stereoisomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, wherein

W is a bond, —C(=S)—, —S(O)—, —$S(O)_2$—, —C(=O)—, —O—, —$C(R^6)(R^7)$—, —$N(R^5)$— or —$C(=N(R^5))$—;

X is —O—, —$N(R^5)$— or —$C(R^6)(R^7)$—; provided that when X is —O—, U is not —O—, —S(O)—, —$S(O)_2$—, —C(=O)— or —$C(=NR^5)$—;

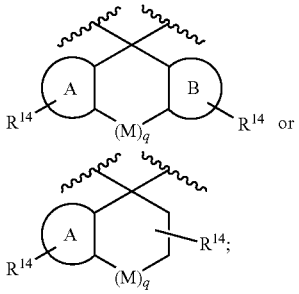
U is a bond, —S(O)—, —$S(O)_2$—, —C(O)—, —O—, —$P(O)(OR^{15})$—, —$C(=NR^5)$—, —$(C(R^6)(R^7))_b$— or —$N(R^5)$—; wherein b is 1 or 2; provided that when W is —S(O)—, —$S(O)_2$—, —O—, or —$N(R^5)$—, U is not —S(O)—, —$S(O)_2$—, —O—, or —$N(R^5)$—; provided that when X is —$N(R^5)$— and W is —S(O)—, —$S(O)_2$—, —O—, or —$N(R^5)$—, then U is not a bond;

R^1, R^2 and R^5 are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, —OR^{15}, —CN, —C(O)R^8, —C(O)OR^9, —S(O)R^{10}, —$S(O)_2R^{10}$, —C(O)$N(R^{11})(R^{12})$, —S(O)$N(R^{11})(R^{12})$, —$S(O)_2N(R^{11})(R^{12})$, —NO_2, —$N{=}C(R^8)_2$ and —$N(R^8)_2$, provided that R^1 and R^5 are not both selected from —NO_2, —$N{=}C(R^8)_2$ and —$N(R^8)_2$;

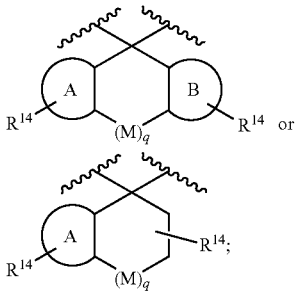
R^3, R^4, R^6 and R^7 are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CH_2—O—$Si(R^9)(R^{10})(R^{19})$, —SH, —CN, —OR^9, —C(O)R^8, —C(O)OR^9, —C(O)$N(R^{11})(R^{12})$, —SR^{19}, —S(O)$N(R^{11})(R^{12})$, —$S(O)_2N(R^{11})(R^{12})$, —$N(R^{11})(R^{12})$, —$N(R^{11})$C(O)R^8, —$N(R^{11})$S(O)R^{10}, —$N(R^{11})$C(O)$N(R^{12})(R^{13})$, —$N(R^{11})$C(O)OR^9 and —C(=NOH)R^8; provided that when U is —O— or —$N(R^5)$—, then R^3, R^4, R^6 and R^7 are not halo, —SH, —OR^9, —SR^{19}, —S(O)$N(R^{11})(R^{12})$, —$S(O)_2N(R^{11})(R^{12})$, —$N(R^{11})(R^{12})$, —$N(R^{11})$C(O)R^8, —$N(R^{11})$S(O)R^{10}, —$N(R^{11})$C(O)$N(R^{12})(R^{13})$, or —$N(R^{11})$C(O)OR^9; provided that when W is —O— or —$N(R^5)$—, then R^3 and R^4 are not halo, —SH, —OR^9, —SR^{19}, —S(O)$N(R^{11})(R^{12})$, —$S(O)_2N(R^{11})(R^{12})$, —$N(R^{11})(R^{12})$, —$N(R^{11})$C(O)R^8, —$N(R^{11})$S(O)R^{10}, —$N(R^{11})$C(O)$N(R^{12})(R^{13})$, or —$N(R^{11})$C(O)OR^9;

and provided that when X is —$N(R^5)$—, W is —C(O)— and U is a bond, R^3, R^4, R^6 and R^7 are not halo, —CN, —SH, —OR^9, —SR^{19}, —S(O)$N(R^{11})(R^{12})$ or —$S(O)_2N(R^{11})(R^{12})$; or R^3, R^4, R^6 and R^7, together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group optionally substituted by R^{14} or a 3-7 membered cycloalkylether optionally substituted by R^{14}

or R^3 and R^4 or R^6 and R^7 together with the carbon to which they are attached, are combined to form multicyclic groups such as



wherein M is —CH_2—, S, —$N(R^{19})$— or O, A and B are independently aryl or heteroaryl and q is 0, 1 or 2 provided that when q is 2, one M must be a carbon atom and when q is 2, M is optionally a double bond; and with the proviso that when R^3, R^4, R^6 and R^7 form said multicyclic groups



then adjacent R^3 and R^4 or R^6 and R^7 groups cannot be combined to form said multicyclic groups;

R^6 is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, —OR^{15}, —$N(R^{15})(R^{16})$, —$N(R^{15})$C(O)R^{16}, —$N(R^{15})$S(O)R^{16}, —$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})$S(O)$N(R^{16})(R^{17})$, —$N(R^{15})$C(O)$N(R^{16})(R^{17})$ and —$N(R^{15})$C(O)OR^{16};

R^9 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

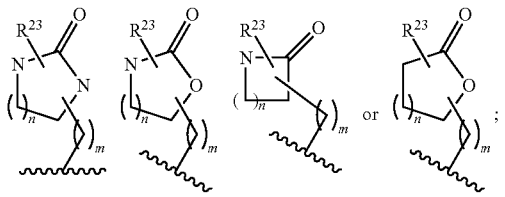
R^{10} is independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and —$N(R^{15})(R^{16})$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, —C(O)R^8, —C(O)OR^9, —S(O)R^{10}, —$S(O)_2R^{10}$, —C(O)$N(R^{15})(R^{16})$, —S(O)$N(R^{15})(R^{16})$, —$S(O)_2N(R^{15})(R^{16})$ and —CN;

R^{14} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CN, —OR^{15}, —C(O)R^{15}, —C(O)OR^{15}, —C(O)$N(R^{15})(R^{16})$, —SR^{15}, —S(O)$N(R^{15})(R^{16})$, —$S(O)_2N(R^{15})(R^{16})$, —C(=NOR^{15})R^{16}, —$P(O)(OR^{15})(OR^{16})$, —$N(R^{15})(R^{16})$, —$N(R^{15})$C(O)R^{16}, —$N(R^{15})$S(O)R^{16}, —$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})$S(O)$N(R^{16})(R^{17})$, —$N(R^{15})$C(O)$N(R^{16})(R^{17})$ and —$N(R^{15})$C(O)OR^{16};

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, arylheterocycloalkyl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocycloalkyl, R^{18}-heterocycloalkylalkyl, R^{18}-aryl, R^{18}-arylalkyl, R^{18}-heteroaryl and R^{18}-heteroarylalkyl; or

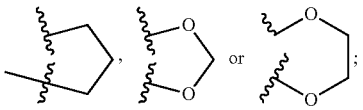
R^{15}, R^{16} and R^{17} are



wherein R^{23} numbers 0 to 5 substituents, m is 0 to 6 and n is 1 to 5;

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, —NO_2, halo, heteroaryl, HO-alkyoxyalkyl, —CF_3, —CN, alkyl-CN, —$C(O)R^{19}$, —C(O)OH, —$C(O)OR^{19}$, —$C(O)NHR^{20}$, —$C(O)NH_2$, —$C(O)NH_2$—C(O)N(alkyl)$_2$, —C(O)N(alkyl)(aryl), —C(O)N(alkyl)(heteroaryl), —SR^{19}, —$S(O)_2R^{20}$, —$S(O)NH_2$, —S(O)NH(alkyl), —S(O)N(alkyl)(alkyl), —S(O)NH(aryl), —$S(O)_2NH_2$, —$S(O)_2NHR^{19}$, —$S(O)_2NH$(heterocycloalkyl), —$S(O)_2N$(alkyl)$_2$, —$S(O)_2N$(alkyl)(aryl), —OCF_3, —OH, —OR^{20}, —O-heterocycloalkyl, —O-cycloalkylalkyl, —O-heterocycloalkylalkyl, —NH_2, —NHR^{20}, —N(alkyl)$_2$, —N(arylalkyl)$_2$, —N(arylalkyl)-(heteroarylalkyl), —$NHC(O)R^{20}$, —$NHC(O)NH_2$, —NHC(O)NH(alkyl), —NHC(O)N(alkyl)(alkyl), —N(alkyl)C(O)NH(alkyl), —N(alkyl)C(O)N(alkyl)(alkyl), —$NHS(O)_2R^{20}$, —$NHS(O)_2NH$(alkyl), —$NHS(O)_2N$(alkyl)(alkyl), —N(alkyl)$S(O)_2NH$(alkyl) and —N(alkyl)$S(O)_2N$(alkyl)(alkyl);

or two R^{18} moieties on adjacent carbons can be linked together to form

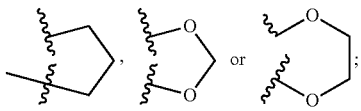


R^{19} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R^{20} is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or heteroarylalkyl;

and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CN, —OR^{15}, —C(O)R^{15}, —$C(O)OR^{15}$, —$C(O)N(R^{15})(R^{16})$, —SR^{15}, —S(O)N$(R^{15})(R^{16})$, —$CH(R^{15})(R^{16})$, —$S(O)_2N(R^{15})(R^{16})$, —$C(=NOR^{15})R^{16}$, —$P(O)(OR^{15})(OR^{16})$, —$N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, —$N(R^{15})C(O)R^{16}$, —CH_2—$N(R^{15})C(O)R^{16}$, —CH_2—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$CH_2$—$R^{15}$; —$CH_2N(R^{15})(R^{16})$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —$CH_2$—$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$, —$CH_2$—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)OR^{16}$, —$CH_2$—$N(R^{15})C(O)OR^{16}$, —S(O)$R^{15}$, =$NOR^{15}$, —$N_3$, —$NO_2$ and —$S(O)_2R^{15}$; and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{21} are independently unsubstituted or substituted by 1 to 5 R^{22} groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, —CF_3, —CN, —OR^{15}, —C(O)R^{15}, —$C(O)OR^{15}$, -alkyl-$C(O)OR^{15}$, $C(O)N(R^{15})(R^{16})$, —SR^{15}, —S(O)N$(R^{15})(R^{16})$, —$S(O)_2N(R^{15})(R^{16})$, —$C(=NOR^{15})R^{16}$, —$P(O)(OR^{15})(OR^{16})$, —$N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, —$N(R^{15})C(O)R^{16}$, —CH_2—$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —CH_2—$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$, —$CH_2$—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)OR^{16}$, —$CH_2$—$N(R^{15})C(O)OR^{16}$, —$N_3$, =$NOR^{15}$, —$NO_2$, —S(O)$R^{15}$ and —$S(O)_2R^{15}$;

or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to form



and when R^{21} or R^{22} are selected from the group consisting of —$C(=NOR^{15})R^{16}$, —$N(R^{15})C(O)R^{16}$, —CH_2—$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —CH_2—$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$, —$CH_2$—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)OR^{16}$ and —CH_2—$N(R^{15})C(O)OR^{16}$, R^{15} and R^{16} together can be a C_2 to C_4 chain wherein, optionally, one, two or three ring carbons can be replaced by —C(O)— or —N(H)— and R^{15} and R^{16}, together with the atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by R^{23};

R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CN, —OR^{24}, —C(O)R^{24}, —$C(O)OR^{24}$, —$C(O)N(R^{24})(R^{25})$, —SR^{24}, —S(O)N$(R^{24})(R^{25})$, —$S(O)_2N(R^{24})(R^{25})$, —$C(=NOR^{24})R^{25}$, —$P(O)(OR^{24})(OR^{25})$, —$N(R^{24})R^{25}$), -alkyl-$N(R^{24})(R^{25})$, —$N(R^{24})C(O)R^{25}$, —CH_2—$N(R^{24})C(O)R^{25}$, —$N(R^{24})S(O)R^{25}$, —$N(R^{24})S(O)_2R^{25}$, —CH_2—$N(R^{24})S(O)_2R^{25}$, —$N(R^{24})S(O)_2N(R^{25})(R^{26})$, —$N(R^{24})S(O)N(R^{25})(R^{26})$, —$N(R^{24})C(O)N(R^{25})(R^{26})$, —$CH_2$—$N(R^{24})C(O)N(R^{25})(R^{26})$, —$N(R^{24})C(O)OR^{25}$, —$CH_2$—$N(R^{24})C(O)OR^{25}$, —S(O)$R^{24}$ and —$S(O)_2R^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, —CF_3, —CN, —OR^{24}, —C(O)R^{24}, —$C(O)OR^{24}$, alkyl-$C(O)OR^{24}$, $C(O)N(R^{24})(R^{25})$, —SR^{24}, —S(O)N$(R^{24})(R^{25})$, —$S(O)_2N(R^{24})(R^{25})$, —$C(=NOR^{24})R^{25}$, —$P(O)(OR^{24})(OR^{25})$, —$N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, —$N(R^{24})C(O)R^{25}$, —CH_2—$N(R^{24})C(O)R^{25}$, —$N(R^{24})S(O)R^{25}$, —$N(R^{24})S(O)_2R^{25}$, —CH_2—$N(R^{24})S(O)_2R^{25}$, —$N(R^{24})S(O)_2N(R^{25})(R^{26})$, —$N(R^{24})S(O)$

$N(R^{25})(R^{26})$, —$N(R^{24})C(O)N(R^{25})(R^{26})$, —$CH_2$—$N(R^{24})C(O)N(R^{25})(R^{26})$, —$N(R^{24})C(O)OR^{25}$, —$CH_2$—$N(R^{24})C(O)OR^{25}$, —$S(O)R^{24}$ and —$S(O)_2R^{24}$;

R^{24}, R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, R^{27}-alkyl, R^{27}-cycloalkyl, R^{27}-cycloalkylalkyl, R^{27}-heterocycloalkyl, R^{27}-heterocycloalkylalkyl, R^{27}-aryl, R^{27}-arylalkyl, R^{27}-heteroaryl and R^{27}-heteroarylalkyl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, aryl, arylalkyl, —NO_2, halo, —CF_3, —CN, alkyl-CN, —$C(O)R^{28}$, —C(O)OH, —$C(O)OR^{28}$, —$C(O)NHR^{29}$, —$C(O)N(alkyl)_2$, —C(O)N(alkyl)(aryl), —C(O)N(alkyl)(heteroaryl), —SR^{28}, —$S(O)_2R^{29}$, —$S(O)NH_2$, —S(O)NH(alkyl), —S(O)N(alkyl)(alkyl), —S(O)NH(aryl), —$S(O)_2NH_2$, —$S(O)_2NHR^{28}$, —$S(O)_2NH$(aryl), —$S(O)_2NH$(heterocycloalkyl), —$S(O)_2N(alkyl)_2$, —$S(O)_2N$(alkyl)(aryl), —OH, —OR^{29}, —O-heterocycloalkyl, —O-cycloalkylalkyl, —O-heterocycloalkylalkyl, —NH_2, —NHR^{29}, —$N(alkyl)_2$, —$N(arylalkyl)_2$, —N(arylalkyl)(heteroarylalkyl), —$NHC(O)R^{29}$, —$NHC(O)NH_2$, —NHC(O)NH(alkyl), —NHC(O)N(alkyl)(alkyl), —N(alkyl)C(O)NH(alkyl), —N(alkyl)C(O)N(alkyl)(alkyl), —$NHS(O)_2R^{29}$, —$NHS(O)_2NH$(alkyl), —$NHS(O)_2N$(alkyl)(alkyl), —N(alkyl)$S(O)_2NH$(alkyl) and —N(alkyl)$S(O)_2N$(alkyl)(alkyl);

R^{28} is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl; and

R^{28} is alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

provided that when W is —C(O)— and U is a bond, R^1 is not optionally substituted phenyl, and that when U is —C(O)— and W is a bond, R^5 is not optionally substituted phenyl;

provided that neither R^1 nor R^5 is —C(O)-alkyl-azetidinone or alkyl di-substituted with (—$COOR^{15}$ or —$C(O)N(R^{15})(R^{16})$) and (—$N(R^{15})(R^{18})$, —$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$, or —$N(R^{15})C(O)OR^{16}$);

provided that when R^1 is methyl, X is —$N(R^5)$—, R^2 is H, W is —C(O)— and U is a bond, (R^3, R^4) is not (H, H), (phenyl, phenyl), (H, phenyl), (benzyl, H), (benzyl, phenyl), (i-butyl, H), (i-butyl, phenyl), (OH-phenyl, phenyl), (halophenyl, phenyl), or (CH_3O-phenyl, NO_2-phenyl); and when W is a bond and U is —C(O)—, (R^3, R^4) is not (H, H), (phenyl, phenyl), (H, phenyl), (benzyl, H), (benzyl, phenyl), (i-butyl, H), (i-butyl, phenyl), (OH-phenyl, phenyl), (halophenyl, phenyl), or (CH_3O-phenyl, NO_2-phenyl);

provided that when X is —$N(R^5)$—, R^1 and R^5 are each H, W is —C(O)— and U is a bond, (R^3, R^4) is not (optionally substituted phenyl, optionally substituted benzyl), (optionally substituted phenyl, heteroarylalkyl) or (heteroaryl, heteroarylalkyl);

provided that when U is a bond, W is —C(O)—, and R^3 and R^4 form a ring with the carbon to which they are attached, R^1 is not 2-CF_3-3-CN-phenyl;

provided that when X is —$N(R^5)$—, U is —O— and W is a bond or —$C(R^6)(R^7)$—, (R^3,R^4) is not (H, —NHC(O)-alkyl-heteroaryl) or (H, alkyl-NHC(O)-alkyl-heteroaryl); and

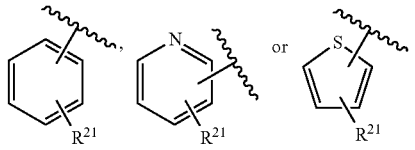
provided that when X is —$N(R^5)$—, R^1 and R^5 are not -alkylaryl-aryl-SO_2—$N(R^{15})(R^{16})$ wherein R^{15} is H and R^{16} is heteroaryl;

provided that when R^1 is R^{21}-aryl or R^{21}-arylalkyl, wherein R^{21} is —OCF_3, —$S(O)CF_3$, —$S(O)_2CF_3$, —S(O)alkyl, —$S(O)_2$alkyl, —$S(O)_2CHF_2$, —$S(O)_2CF_2CF_3$, —OCF^2CHF_2, —$OCHF_2$, —OCH_2CF_3, —SF_5 or —$S(O)_2NR^{15}R^{16}$;

wherein R^{15} and R^{16} are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-heterocycloalkyl, R^{18}-aryl and R^{18}-heteroaryl; U is a bond or —CH_2; and X is —$N(R^5)$—; then R^5 is H;

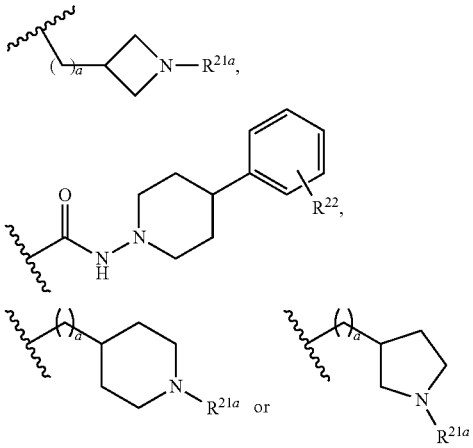
provided that when U is a bond,

R^3 and R^4 are alkyl,



where R^{21} is halo, —CN, alkyl, alkoxy, haloalkyl or haloalkoxy, or R^3 and R^4, together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group,

and R^1 is



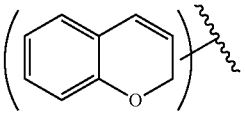
where a is 0 to 6 and R^{22} is alkyl, alkoxy, halo, —CN, —OH, —NO_2 or haloalkyl;

then R^{21a} is not H, —$C(O)_2R^{15}$, wherein R^{15} is selected from the group consisting of alkyl, cycloalkyl and alkyl substituted with phenyl, alkyl or alkyl-R^{22}, wherein R^{22} is selected from the group consisting of

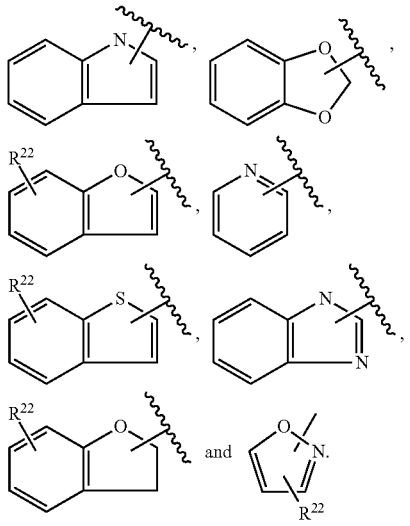
phenyl,

phenyl substituted with alkyl.

and



wherein R^{22} is selected from the group consisting of H, methoxy, nitro, oxo, —OH, halo and alkyl,



In another aspect, the invention relates to a pharmaceutical composition comprising at least one compound of formula I and a pharmaceutically acceptable carrier.

In another aspect, the invention comprises the method of inhibiting aspartyl protease comprising administering at least one compound of formula I to a patient in need of such treatment.

More specifically, the invention comprises: the method of treating a cardiovascular disease such as hypertension, renal failure, or a disease modulated by renin inhibition; the method of treating Human Immunodeficiency Virus; the method of treating a cognitive or neurodegenerative disease such as Alzheimer's Disease; the method of inhibiting plasmepins I and II for treatment of malaria; the method of inhibiting Cathepsin D for the treatment of Alzheimer's Disease, breast cancer, and ovarian cancer; and the method of inhibiting protozoal enzymes, for example inhibition of plasmodium falciparnum, for the treatment of fungal infections. Said method of treatment comprise administering at least one compound of formula I to a patient in need of such treatment. In particular, the invention comprises the method of treating Alzheimer's disease comprising administering at least one compound of formula I to a patient in need of such treatment.

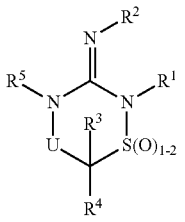
In another aspect, the invention comprises the method of treating Alzheimer's disease comprising administering to a patient I need of such treatment a combination of at least one compound of formula I and a cholinesterase inhibitor or a muscarinic antagonist.

In a final aspect, the invention relates to a kit comprising in separate containers in a single package pharmaceutical compositions for use in combination, in which one container comprises a compound of formula I in a pharmaceutically acceptable carrier and a second container comprises a cholinesterase inhibitor or a muscarinic antagonist in a pharmaceutically acceptable carrier, the combined quantities being an effective amount to treat a cognitive disease or neurodegenerative disease such as Alzheimer's disease.

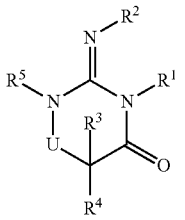
DETAILED DESCRIPTION

Compounds of formula I wherein X, W and U are as defined above include the following independently preferred structures:

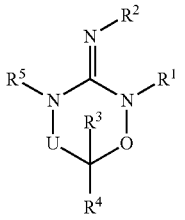
IA



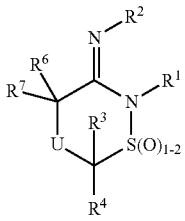
IB



IC



ID



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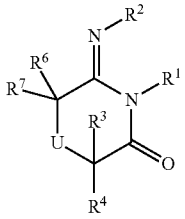

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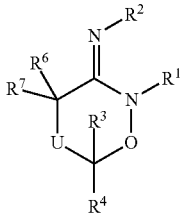
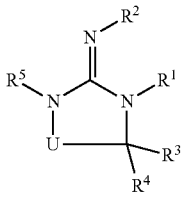


IG



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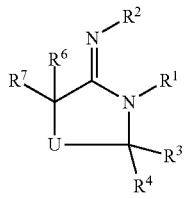
IH



In compounds of formulas IA to IF, U is preferably a bond or —C(R^6)(R^7)—. In compounds of formula IG and IH, U is preferably —C(O)—.

It will be understood that since the definition of R^1 is the same as the definition of R^5, when X is —N(R^5)—, compounds of formula I wherein W is a bond and U is a bond, —S(O)—, —S(O)$_2$—, —C(O)—, —O—, —C(R^6)(R^7)— or —N(R^5)— are equivalent to compounds of formula I wherein U is a bond and W is a bond, —S(O)—, —S(O)$_2$—, —C(O)—, —O—, —C(R^6)(R^7)— or —N(R^5)—.

More preferred compounds of the invention are those of formula IB wherein U is a bond or those of formula IB wherein U is —C(R^6)(R^7)—.

Another group of preferred compounds of formula I is that wherein R^2 is H.

R^3, R^4, R^6 and R^7 are preferably selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CH$_2$—O—Si(R^9)(R^{10})(R^{19}), —SH, —CN, —OR^9, —C(O) R^8, —C(O)OR^9, —C(O)N(R^{11})(R^{12}), —SR^{19}, —S(O)N(R^{11})(R^{12}), —S(O)$_2$N(R^{11})(R^{12}), —N(R^{11})(R^{12}), —N(R^{11})C(O)R^8, —N(R^{11})S(O)R^{10}, —N(R^{11})C(O)N(R^{12})(R^{13}), —N(R^{11})C(O)OR^9 and —C(=NOH)R^8.

R^3, R^4, R^6 and R^7 are preferably selected from the group consisting of aryl, heteroaryl, heteroarylalkyl, arylalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkyl and cycloalkylalkyl.

In a group of preferred compounds

U is a bond or —C(O)—;

W is a bond or —C(O)—;

X is —N(R^5)—;

R^1 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkyalkyl or R^{21}-heterocycloalkylalkyl,

R^2 is H;

R^3 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

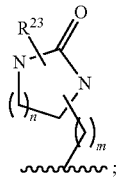
R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

R^5 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkyalkyl or R^{21}-heterocycloalkylalkyl;

R^6 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

R^7 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

R^{15}, R^{16} and R^{17} is H, R^{18}-alkyl, alkyl or



R^{21} is alkyl, aryl, halo, —OR^{15}, —NO_2, —C(O)R^{15}, —CH_2—N(R^{15})C(O)N(R^{16})(R^{17}) or —CH(R^{15})(R^{16});

n is 1;

m is 1;

R^{18} is —OR^{20}

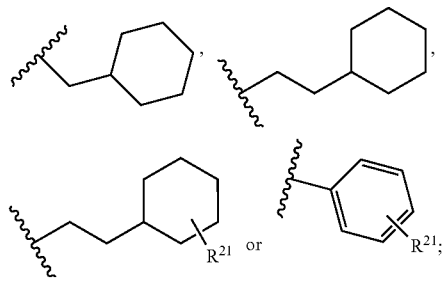
R^{20} is aryl;

and

R^{23} is alkyl.

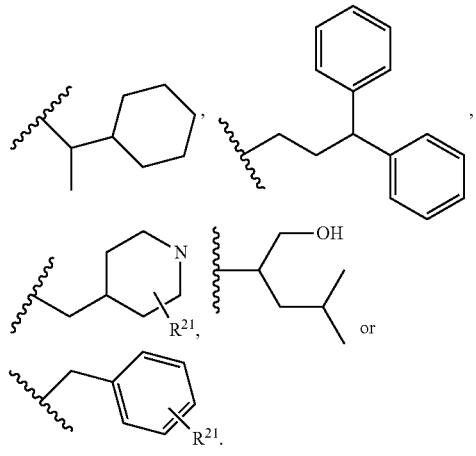
In a group of preferred compounds

R^3, R^4, R^6 and R^7 are



and

R^1 and R^5 is H, CH_3,



In an additional group of preferred compounds;

U is a bond or —C(O)—;

W is a bond or —C(O)—;

X is —N(R^5)—;

R^1 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkyalkyl or R^{21}-heterocycloalkylalkyl,

R^2 is H;

R^3 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl,

R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

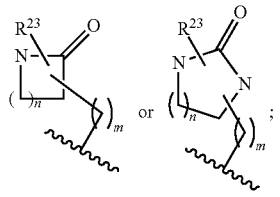
R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^5 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkyalkyl or R^{21}-heterocycloalkylalkyl;

R^6 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^7 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^{15}, R^{16} and R^{17} is H, cycloalkyl, cycloalkylalkyl, R^{18}-alkyl, alkyl, aryl, R^{18}-aryl, R^{18}-arylalkyl, arylalkyl,



n is 1 or 2;

m is 0 or 1;

R^{18} is —OR^{20} or halo;

R^{20} is aryl or halo substituted aryl;

R^{21} is alkyl, aryl, heteroaryl, R^{22}-alkyl, R^{22}-aryl, R^{22}-heteroaryl, halo, heterocycloalkyl, —$N(R^{15})(R^{16})$, —OR^{15}, —NO_2, —$C(O)R^{15}$, —$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —CH_2—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$ or —$CH(R^{15})(R^{16})$;

R^{22} is —OR^{15} or halo

and

R^{23} is H or alkyl.

As used above, and throughout the specification, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

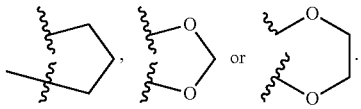
"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl and decyl. R^{32}-substituted alkyl groups include fluoromethyl, trifluoromethyl and cyclopropylmethyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more substituents (e.g., R^{18}, R^{21}. R^{22}, etc.) which may be the same or different, and are as defined herein or two substituents on adjacent carbons can be linked together to form

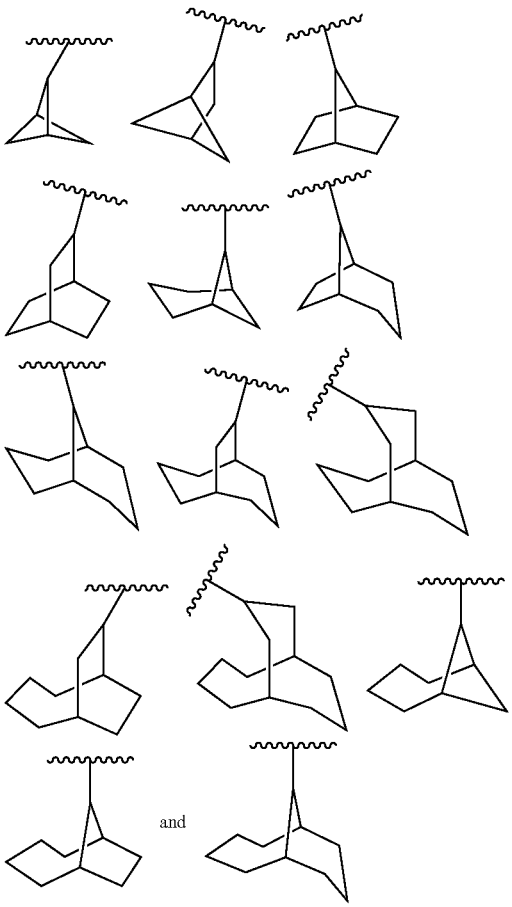


Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one to four of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more R^{21} substituents which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The

cycloalkyl can be optionally substituted with one or more R^{21} substituents which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like. Further non-limiting examples of cycloalkyl include the following



"Cycloalkylether" means a non-aromatic ring of 3 to 7 members comprising an oxygen atom and 2 to 7 carbon atoms. Ring carbon atoms can be substituted, provided that substituents adjacent to the ring oxygen do not include halo or substituents joined to the ring through an oxygen, nitrogen or sulfur atom.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. The cycloalkenyl ring can be optionally substituted with one or more R^{21} substituents which may be the same or different, and are as defined above. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic azaheterocyclenyl groups include 1,2,3,4-tetrahydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Non-limiting examples of suitable oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. Non-limiting example of a suitable multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Non-limiting examples of suitable monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

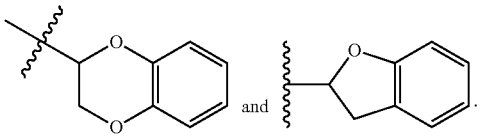
"Heterocyclyl" (or heterocycloalkyl) means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which 1-3, preferably 1 or 2 of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclyl can be optionally substituted by one or more R^{21} substituents which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Arylcycloalkyl" means a group derived from a fused aryl and cycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl and cycloalkyl consists of about 5 to about 6 ring atoms. The arylcycloalkyl can be optionally substituted by 1-5 R^{21} substituents. Non-limiting examples of suitable arylcycloalkyls include indanyl and 1,2,3,4-tetrahydronaphthyl and the like. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylheterocycloalkyl" means a group derived from a fused aryl and heterocycloalkyl as defined herein. Preferred arylcycloalkyls are those wherein aryl is phenyl and heterocycloalkyl consists of about 5 to about 6 ring atoms. The

arylheterocycloalkyl can be optionally substituted by 1-5 R^{21} substituents. Non-limiting examples of suitable arylheterocycloalkyls include



The bond to the parent moiety is through a non-aromatic carbon atom.

Similarly, "heteroarylalkyl" "cycloalkylalkyl" and "heterocycloalkylalkyl" mean a heteroaryl-, cycloalkyl- or heterocycloalkyl-alkyl- group in which the heteroaryl, cycloalkyl, heterocycloalkyl and alkyl are as previously described. Preferred groups contain a lower alkyl group. The bond to the parent moiety is through the alkyl.

"Acyl" means an H—C(O)—, alkyl-C(O)—, alkenyl-C(O)—, alkynyl-C(O)— or cycloalkyl-C(O)— group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and cyclohexanoyl.

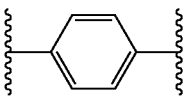
"Alkoxy" means an alkyl-O— group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and heptoxy. The bond to the parent moiety is through the ether oxygen.

"Alkyoxyalkyl" means a group derived from an alkoxy and alkyl as defined herein. The bond to the parent moiety is through the alkyl.

"Arylalkenyl" means a group derived from an aryl and alkenyl as defined herein. Preferred arylalkenyls are those wherein aryl is phenyl and the alkenyl consists of about 3 to about 6 atoms. The arylalkenyl can be optionally substituted by one or more R^{27} substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylalkynyl" means a group derived from a aryl and alkenyl as defined herein. Preferred arylalkynyls are those wherein aryl is phenyl and the alkynyl consists of about 3 to about 6 atoms. The arylalkynyl can be optionally substituted by one or more R^{27} substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

The suffix "ene" on alkyl, aryl, hetercycloalkyl, etc. indicates a divalent moiety, e.g., $—CH_2CH_2—$ is ethylene, and



is para-phenylene.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties, in available position or positions.

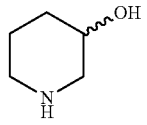
Substitution on a cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, or heteroarylalkyl moiety includes substitution on the ring portion and/or on the alkyl portion of the group.

When a variable appears more than once in a group, e.g., R^8 in $—N(R^8)_2$, or a variable appears more than once in the structure of formula I, e.g., R^{15} may appear in both R^1 and R^3, the variables can be the same or different.

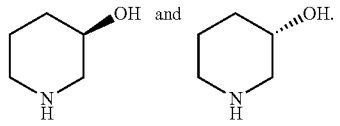
With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within the knowledge of those skilled in the art. With respect to the compositions and methods comprising the use of "at least one compound of formula I," one to three compounds of formula I can be administered at the same time, preferably one.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

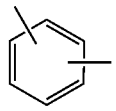
The wavy line ~~~ as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)-stereochemistry. For example,



means containing both

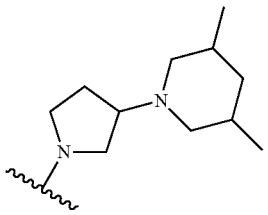


Lines drawn into the ring systems, such as, for example:

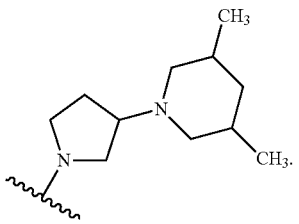


indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:



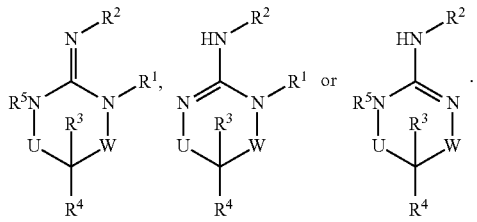
represents



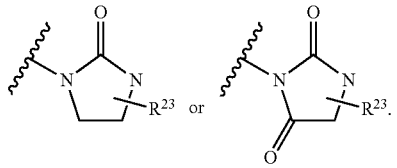
It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae,

and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

Those skilled in the art will recognize that certain compounds of formula I are tautomeric, and all such tautomeric forms are contemplated herein as part of the present invention. For example, a compound wherein X is —N(R^5)— and R^1 and R^5 are each H can be represented by any of the following structures:



When R^{21} and R^{22}, are, for example, —N(R^{15})C(O)N(R^{16})(R^{17}) and R^{15} and R^{16} form a ring, the moiety formed, is, for example,



Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting aspartyl protease and/or inhibiting BACE-1 and thus producing the desired therapeutic effect in a suitable patient.

The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the formula I may be formed, for example, by reacting a compound of formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization. Acids (and bases) which are generally considered suitable for the formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for example, by S. Berge et al, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson et al, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (2002) Int'l Union of Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, methyl sulfates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pamoates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, aluminum salts, zinc salts, salts with organic bases (for example, organic amines) such as benzathines, diethylamine, dicyclohexylamines, hydrabamines (formed with N,N-bis (dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, piperazine, phenylcyclohexylamine, choline, tromethamine, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various sub-

stituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of formula I, and of the salts, solvates and prodrugs of the compounds of formula I, are intended to be included in the present invention

Compounds of formula I can be made using procedures known in the art. Preparative methods for preparing starting materials and compounds of formula I are show below as general reaction schemes (Method A, Method B, etc.) followed by specific procedures, but those skilled in the art will recognize that other procedures can also be suitable. In the Schemes and in the Examples below, the following abbreviations are used:

methyl: Me; ethyl: Et; propyl: Pr; butyl: Bu; benzyl: Bn; tertiary butyloxycarbonyl: Boc or BOC

high pressure liquid chromatography: HPLC

liquid chromatography mass spectroscopy: LCMS

room temperature: RT or rt

day: d; hour: h; minute: min

retention time: R_t

microwave: μW

saturated: sat.; anhydrous: anhyd.

1-hydroxybenzotriazole: HOBt

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: EDCl

ethyl acetate: EtOAc

Benzyloxycarbonyl: CBZ

[1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)]: Selectfluor

1,8-diazabicyclo[5,4,0]undec-7-ene: DBU

tetrahydrofuran: THF; N,N-dimethylformamide: DMF; methanol: MeOH; diethyl ether: Et_2O; acetic acid: AcOH; acetonitrile: MeCN; trifluoroacetic acid: TFA; dichloromethane: DCM; dimethoxyethane: DME; diphenylphosphinoferrocene (dppf);

n-butyllithium: n-BuLi; lithium diisopropylamide: LDA

1-hydroxy-7-azabenzotriazole: HOAt

4-N,N-dimethylaminopyridine: DMAP; diisopropylethylamine: DIEA; N-methylmorpholine: NMM

Microporous Toluene sulfonic acid resin (MP-TsOH resin)

tris-(2-aminoethyl)aminomethyl polystyrene (PS-trisamine)

methylisocyanate polystyrene (PS-NCO)

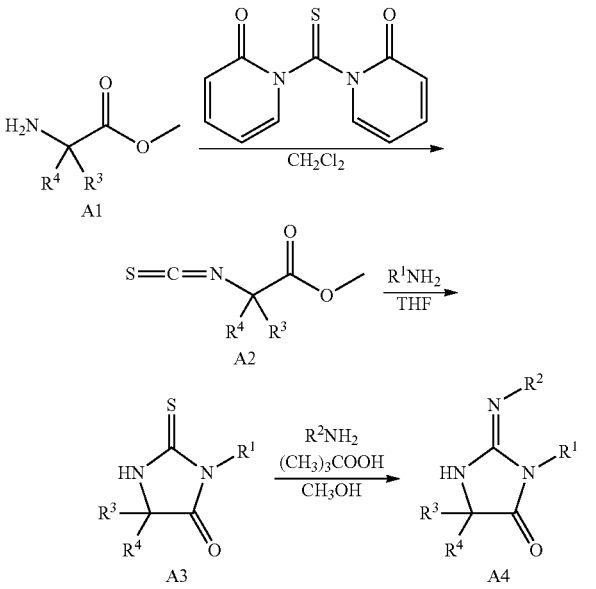
Saturated (sat.); anhydrous. (anhyd); room temperature (rt); hour (h); Minutes (Min), Retention Time (R_t); molecular weight (MW); milliliter (mL); gram (g). milligram (mg); equivalent (eq); day (d); microwave (μW); microliter (μL);

All NMR data were collected on 400 MHz NMR spectrometers unless otherwise indicated. LC-Electrospray-Mass spectroscopy with a C-18 column and 5% to 95% MeCN in water as the mobile phase was used to determine the molecular mass and retention time. The tables contain the compounds with retention time/observed MW and/or NMR data.

For internal consistency in the reaction schemes shown in Methods A to AA, the product of each method is shown as structure A4, B4, C3, etc., wherein certain variables are as defined for that method, but it will be apparent that, for example, A4 has the same structure as C3. That is, different methods can be used to prepare similar compounds.

The compounds in the invention may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below. Table I contains the compounds with observed m/e values from mass spectrascopy and/or NMR data. These compounds can be obtained with synthetic methods similar to these listed in the last column using appropriate reagents.

Method A



Method A, Step 1:

To a solution of A1 (R^3=CH_3 & R^4=$CH_2CH(CH_3)_2$) (10 mmol, 1 eq) in 30 ml of anhyd. CH_2Cl_2 was added thiocarbonyl dipyridone (1.2 eq). After stirring overnight the solution was diluted with CH_2Cl_2, washed with 1N HCl, H_2O (2×), and a saturated aqueous NaCl solution (2×). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography to afford A2 (R^3=CH_3 & R^4=$CH_2CH(CH_3)_2$).

Method A, Step 2:

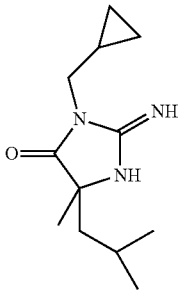
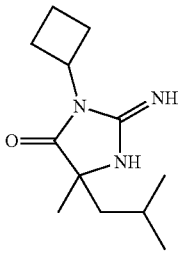
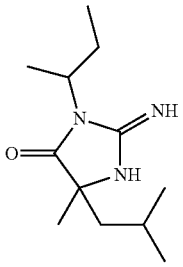
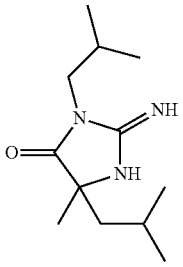
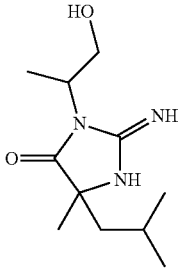
A solution of 3,5-difluorobenzyl amine (0.15 mmol, 1.5 eq) in THF (0.15 mL) was added to a solution of A2 (R^3=CH_3 & R^4=$CH_2CH(CH_3)_2$) (0.1 mmol, 1 eq) in anhydrous CH_2Cl_2 (1 mL). The reaction mixture was refluxed overnight. The reaction solution was added to MP-TsOH resin (2-3 eq) and diluted with CH_3CN. The suspension was agitated overnight. The mixture was filtered and the filtrate was concentrated to afford A3 (R^1=3,5-difluorobenzyl, R^3=CH_3, & R^4=$CH_2CH(CH_3)_2$).

Method A, Step 3:

To a solution of A3 (R^1=3,5-difluorobenzyl, R^3=CH_3, & R^4=$CH_2CH(CH_3)_2$) (10 mg) in CH_3OH (1 mL) was added NH_4OH (0.44 mL) and t-butyl hydrogen peroxide (0.1 mL) and the reaction mixture was agitated for 2 d. The solution was concentrated, the resulting residue was dissolved in

CH_3OH (1.2 mL) and was treated with sulfonic acid resin. The suspension was agitated overnight and the resin was washed with CH_3OH (4×10 min) before it was treated with 2 N NH_3 in CH_3OH for 1 h. The suspension was filtered and the filtrate was concentrated to give the crude material which was purified by preparative HPLC/LCMS eluting with a CH_3CN/H_2O gradient to afford A4 (R^1=3,5-difluorobenzyl, R^2=H, R^3=CH_3, & R^4=$CH_2CH(CH_3)_2$). NMR (CD_3OD): δ6.9, m, 3H; δ4.8-4.9, m; δ1.75, d, 2H; δ1.5, m, 1H; δ1.42, s, 3H; δ0.85, d, 3H; δ0.65, d, 3H. ES_LCMS (m/e) 296.1.

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e
1		223	224
2		223	224
3		225	226
4		225	226
5		227	228

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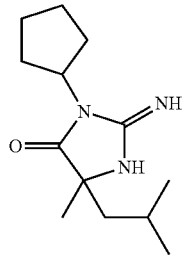
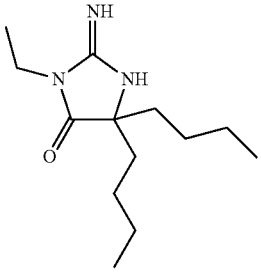
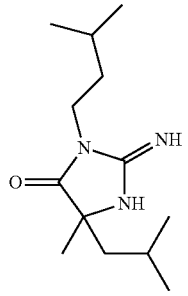
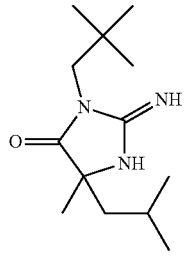
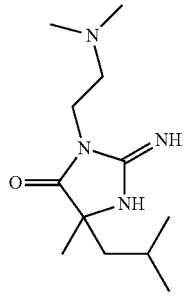
#	Structure	MW	Obs. m/e
6		237	238
7		239	240
8		239	240
9		239	240
10		240	241

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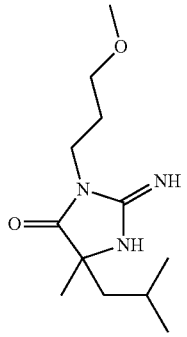
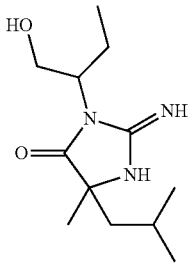
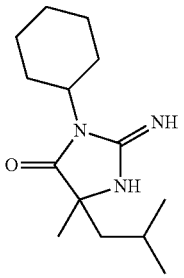
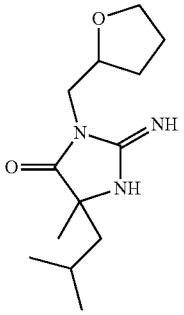
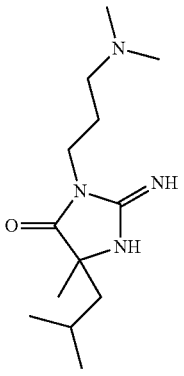
#	Structure	MW	Obs. m/e
11		241	242
12		241	242
13		251	252
14		253	254
15		254	255

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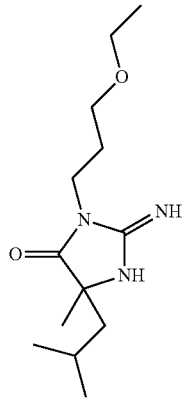
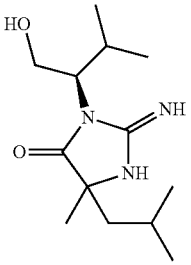
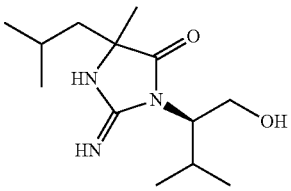
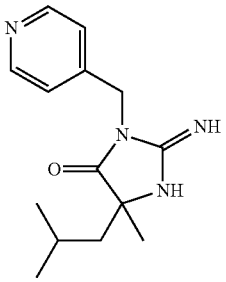
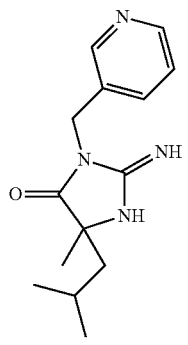
#	Structure	MW	Obs. m/e
16		255	256
17		255	256
18		255	256
19		260	261
20		260	261

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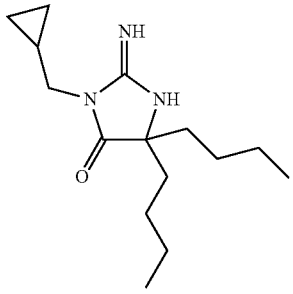
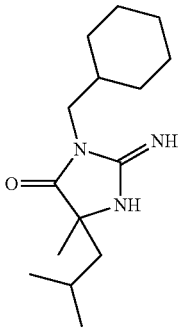
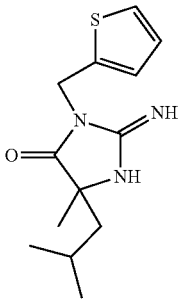
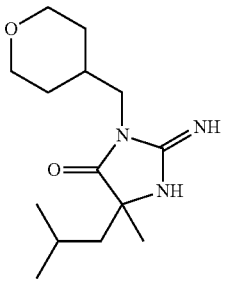
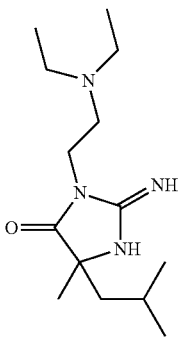
#	Structure	MW	Obs. m/e
21		265	266
22		265	266
23		265	266
24		267	268
25		268	269

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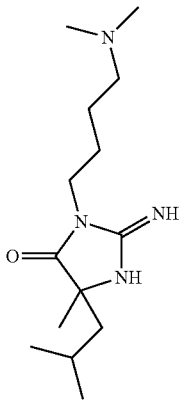
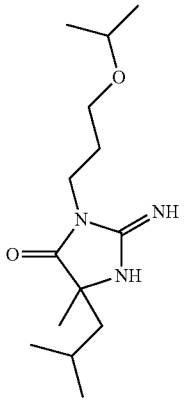
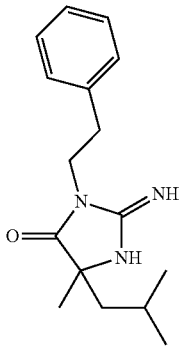
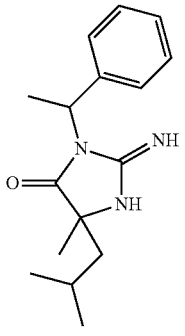
#	Structure	MW	Obs. m/e
26		268	269
27		269	270
28		273	274
29		273	274

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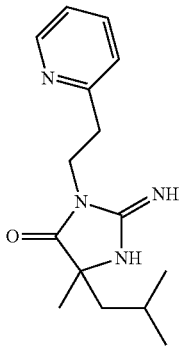
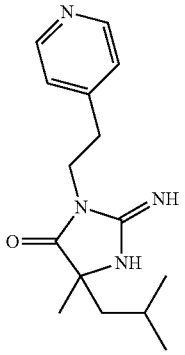
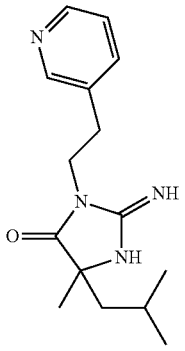
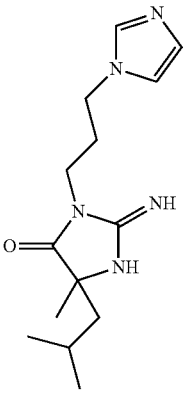
#	Structure	MW	Obs. m/e
30		274	275
31		274	275
32		274	275
33		277	278

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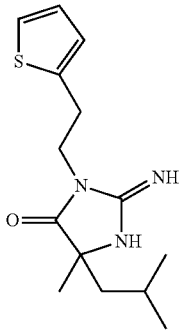
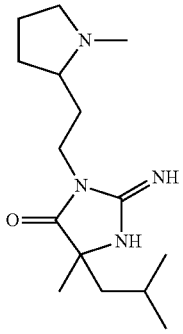
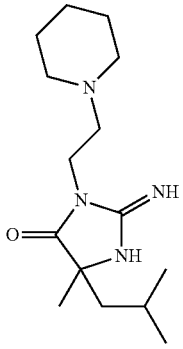
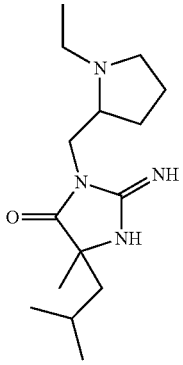
#	Structure	MW	Obs. m/e
34		279	280
35		280	281
36		280	281
37		280	281

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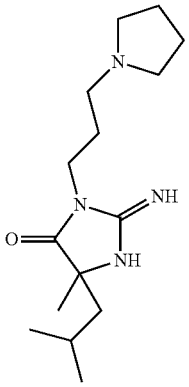
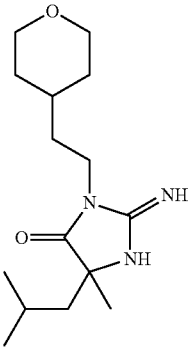
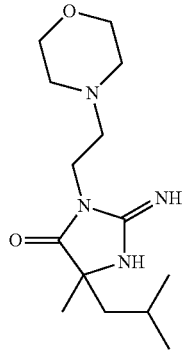
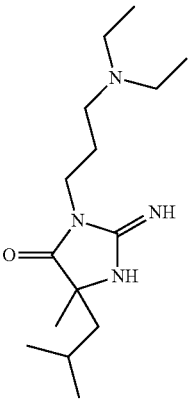
#	Structure	MW	Obs. m/e
38		280	281
39		281	282
40		282	283
41		282	283

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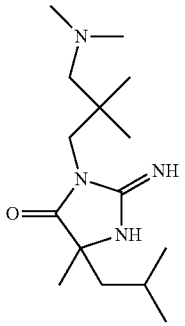
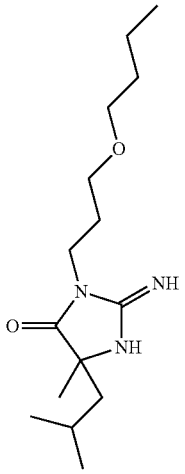
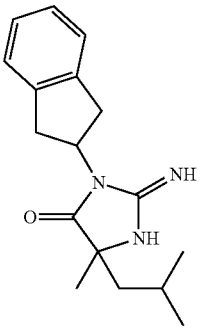
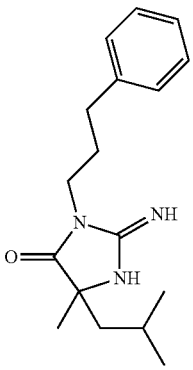
#	Structure	MW	Obs. m/e
42		282	283
43		283	284
44		285	286
45		287	288

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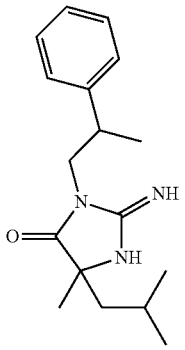
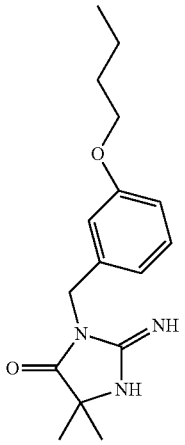
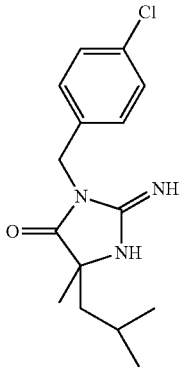
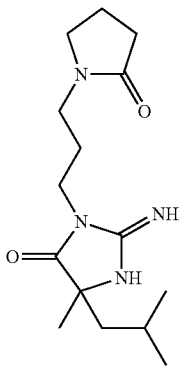
#	Structure	MW	Obs. m/e
46		287	288
47		289	290
48		293	294
49		294	295

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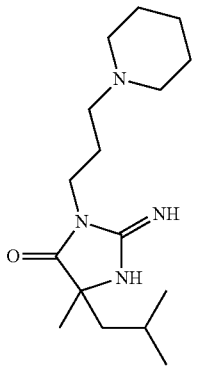
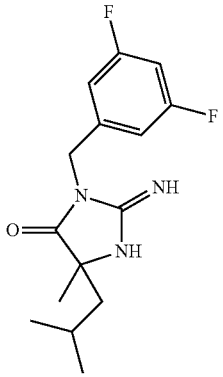
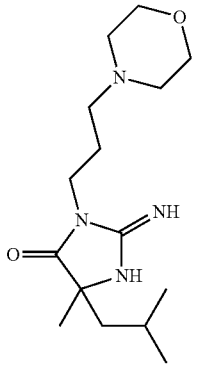
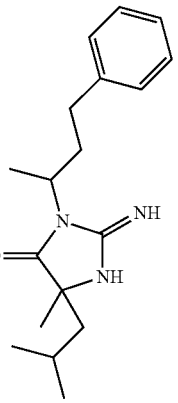
#	Structure	MW	Obs. m/e
50		294	295
51		295	296
52		296	297
53		301	302

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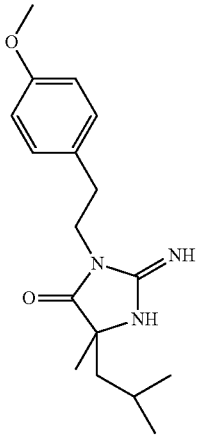
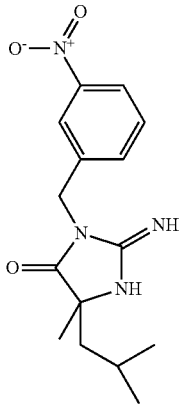
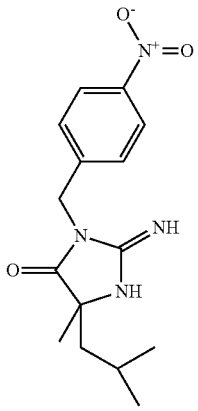
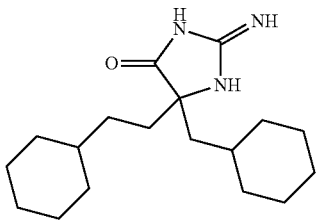
#	Structure	MW	Obs. m/e
54		303	304
55		304	305
56		304	305
57		305	306

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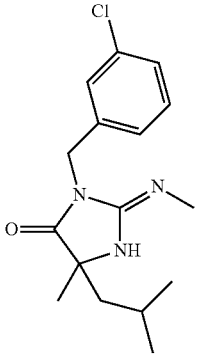
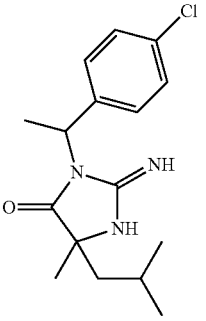
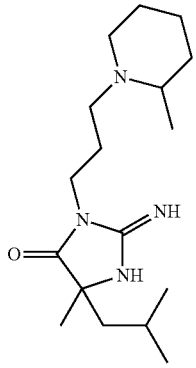
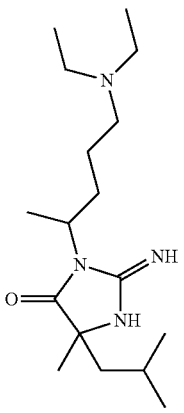
#	Structure	MW	Obs. m/e
58		307	308
59		307	308
60		308	309
61		310	311

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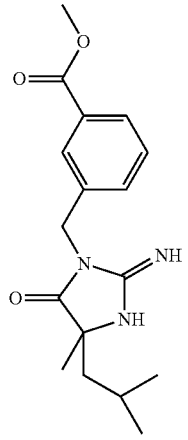
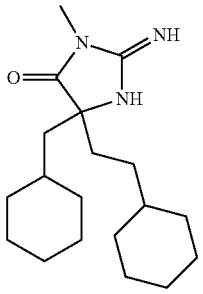
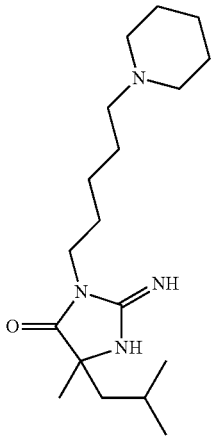
#	Structure	MW	Obs. m/e
62		317	318
63		319	320
64		322	323

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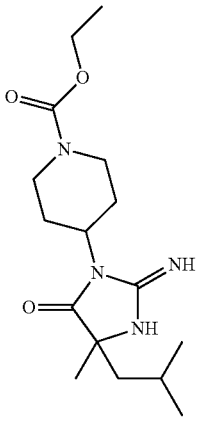
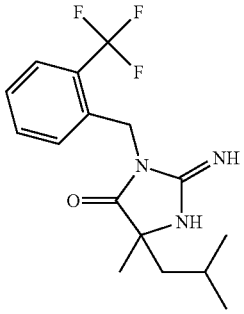
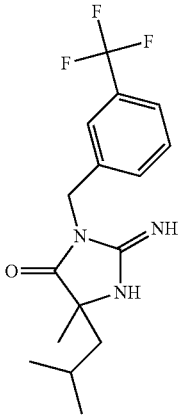
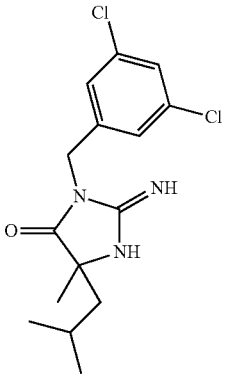
#	Structure	MW	Obs. m/e
65		324	325
66		327	328
67		327	328
68		327	328

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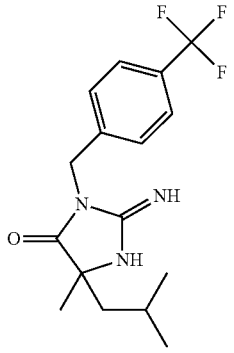
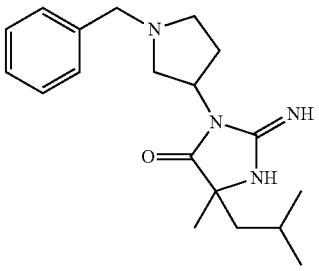
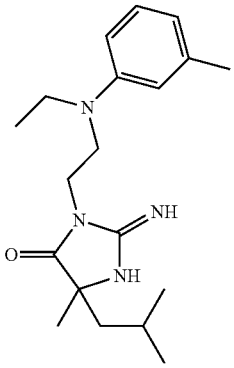
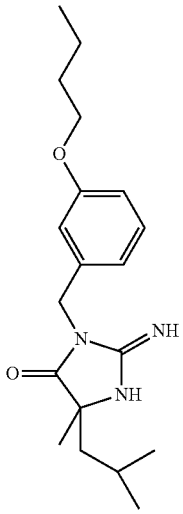
#	Structure	MW	Obs. m/e
69		327	328
70		328	329
71		330	331
72		331	332

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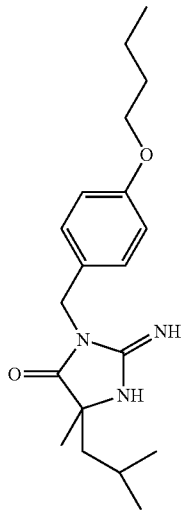
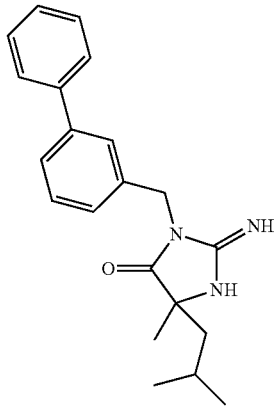
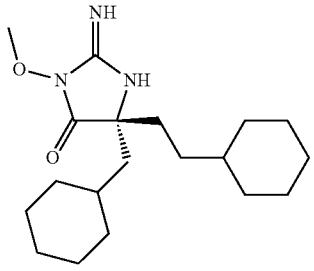
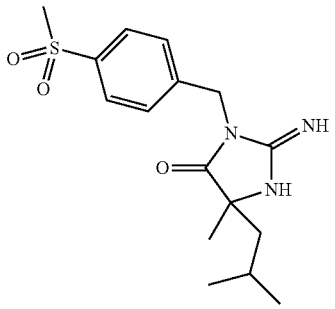
#	Structure	MW	Obs. m/e
73		331	332
74		335	336
75		335	336
76		337	338

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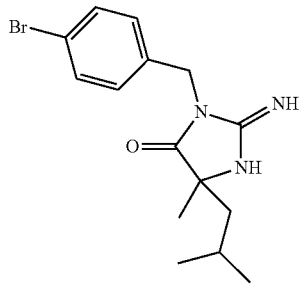
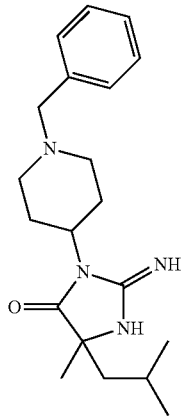
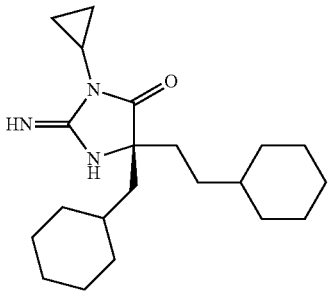
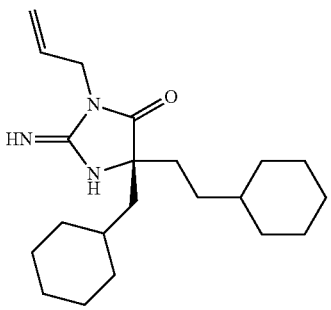
#	Structure	MW	Obs. m/e
77		337	338
78		342	343
79		345	346
80		345	346

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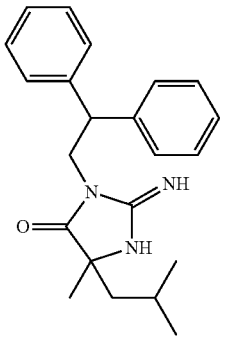
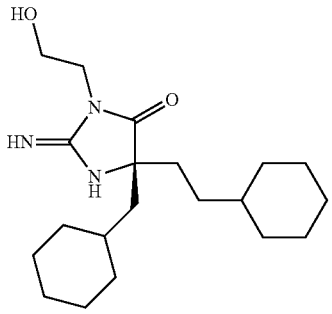
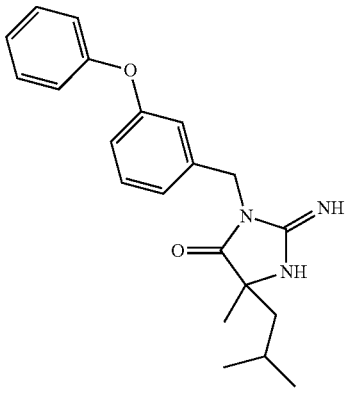
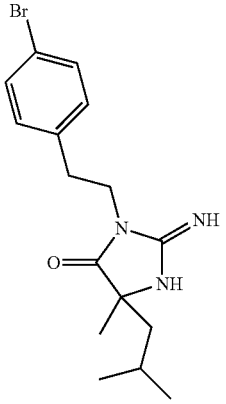
#	Structure	MW	Obs. m/e
81		349	350
82		349	350
83		351	352
84		351	352

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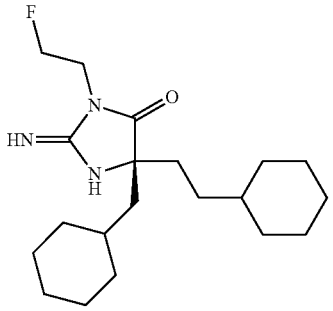
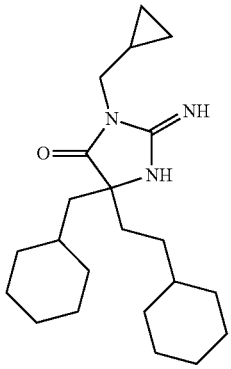
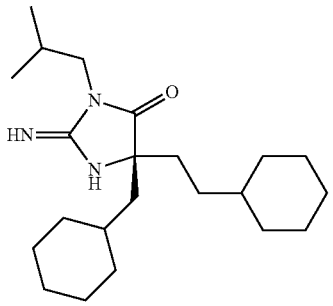
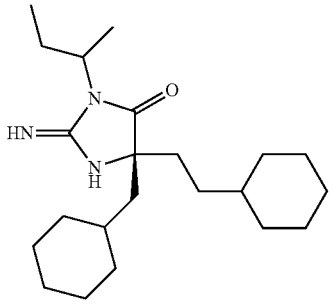
#	Structure	MW	Obs. m/e
85		351	352
86		359	360
87		361	362
88		361	362

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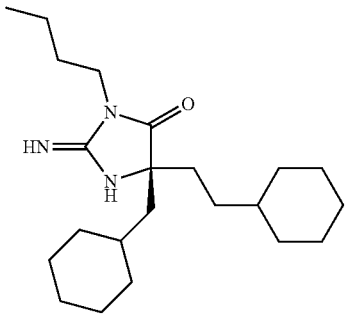
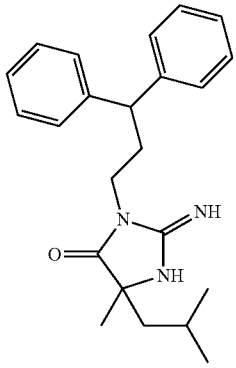
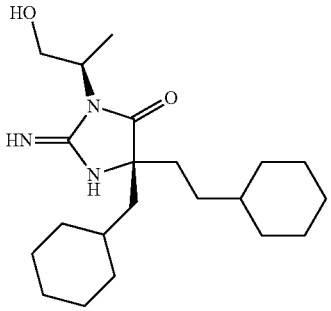
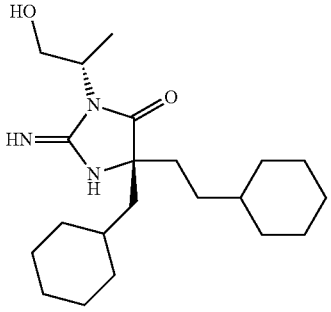
#	Structure	MW	Obs. m/e
89		361	362
90		363	364
91		363	364
92		363	364

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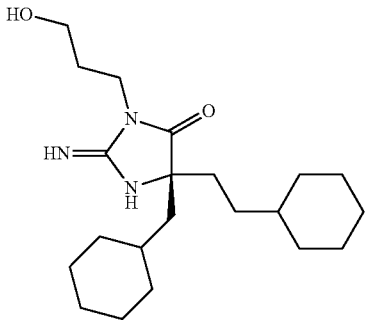
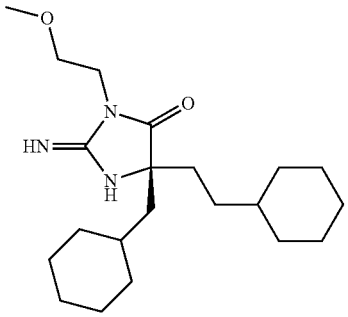
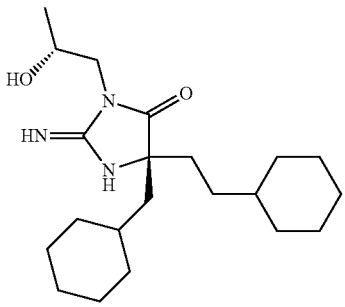
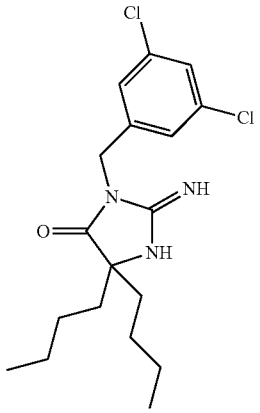
#	Structure	MW	Obs. m/e
93		363	364
94		363	364
95		363	364
96		369	370

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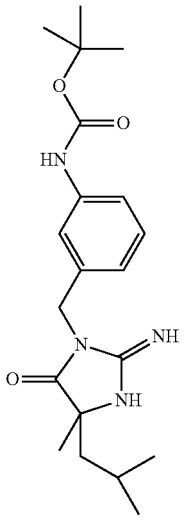
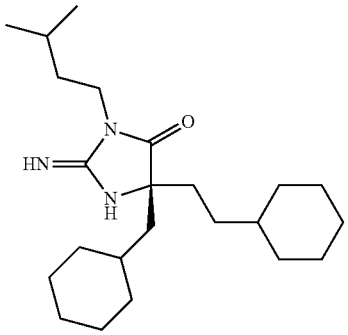
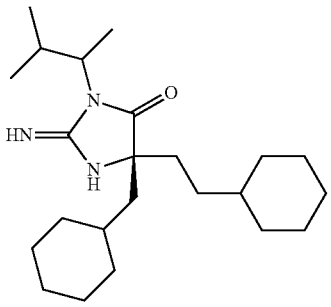
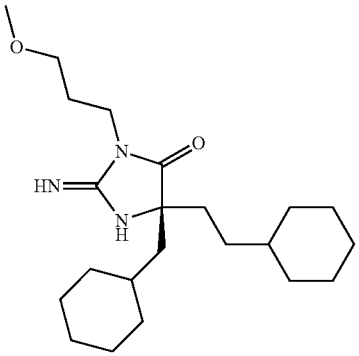
#	Structure	MW	Obs. m/e
97		374	375
98		375	376
99		375	376
100		377	378

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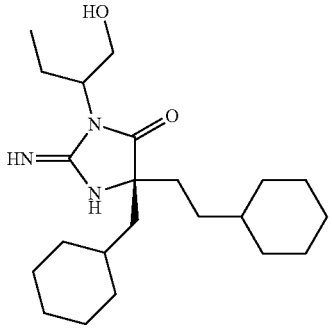
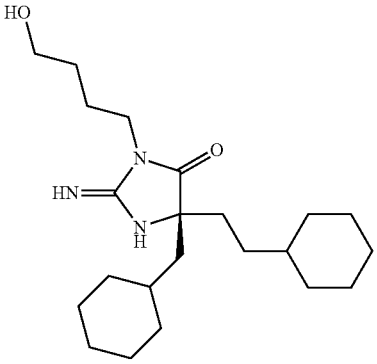
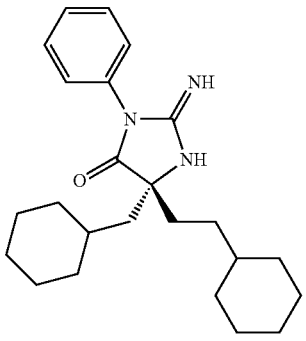
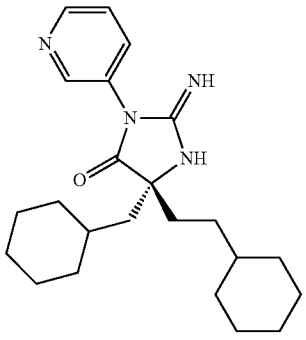
#	Structure	MW	Obs. m/e
101		377	378
102		377	378
103		381	382
104		382	383

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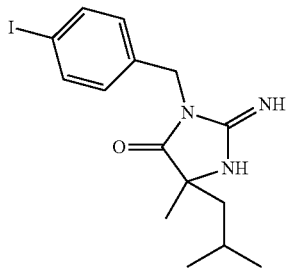
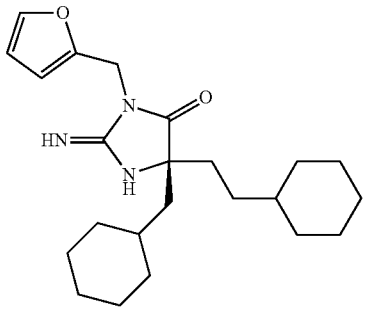
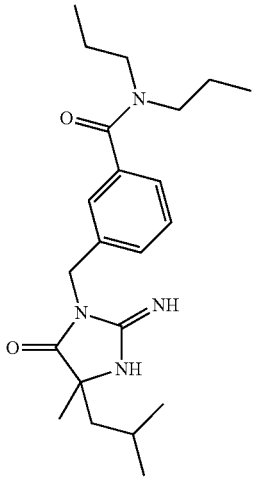
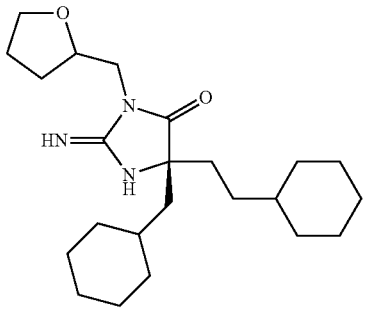
#	Structure	MW	Obs. m/e
105		385	386
106		385	386
107		386	387
108		389	390

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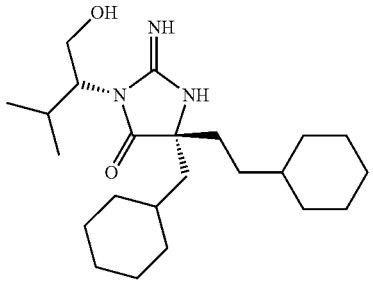
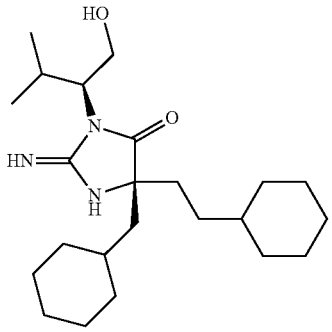
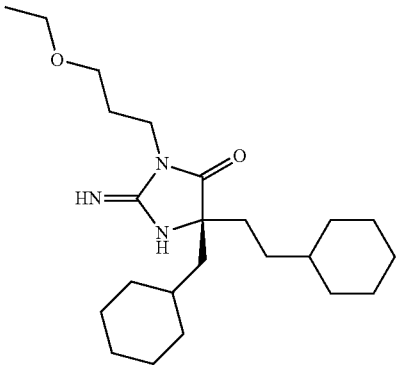
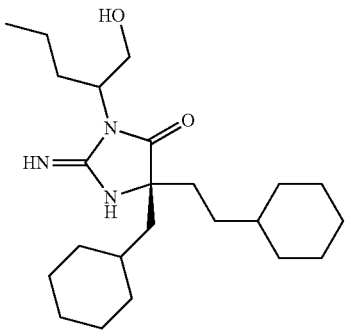
#	Structure	MW	Obs. m/e
109		391	392
110		391	392
111		391	392
112		391	392

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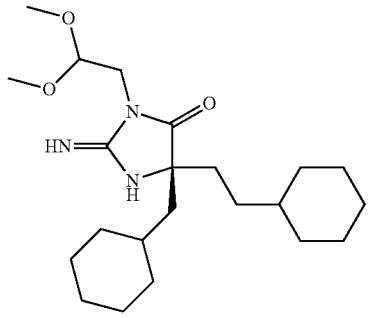
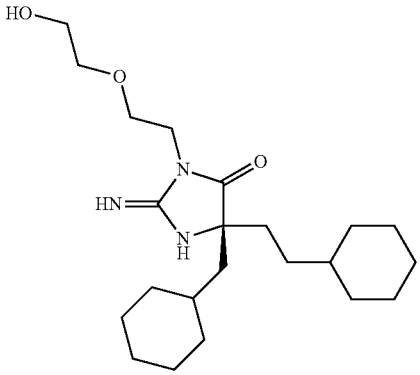
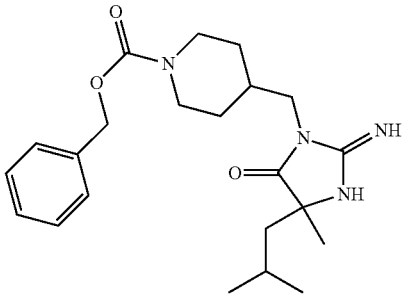
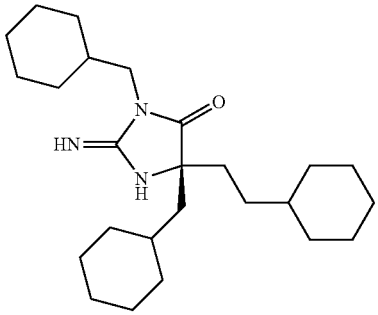
#	Structure	MW	Obs. m/e
113		393	394
114		393	394
115		400	401
116		401	402

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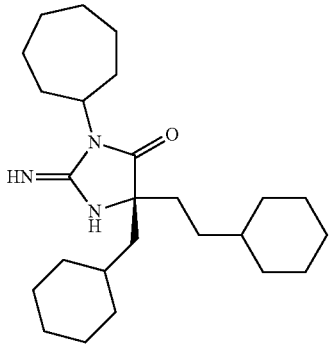
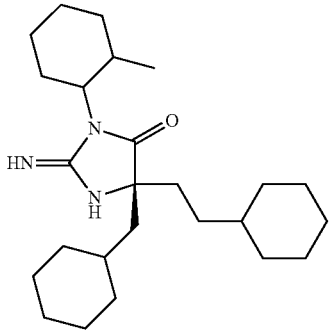
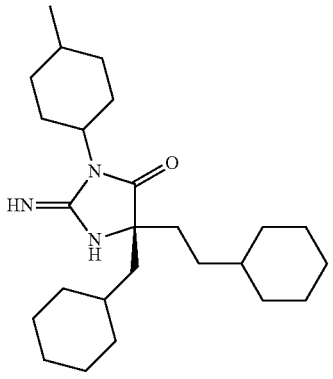
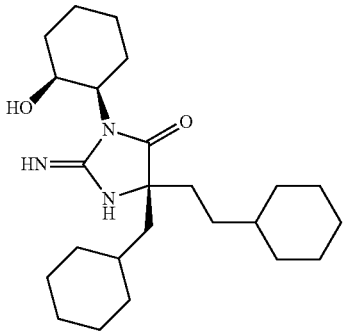
#	Structure	MW	Obs. m/e
117		401	402
118		401	402
119		401	402
120		403	404

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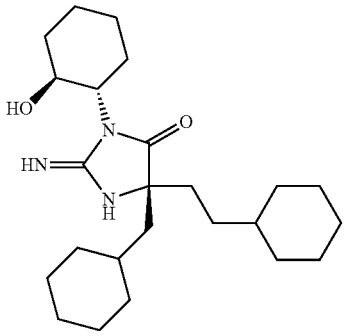
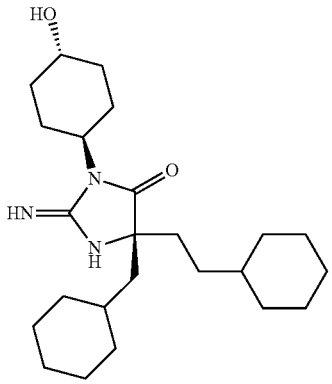
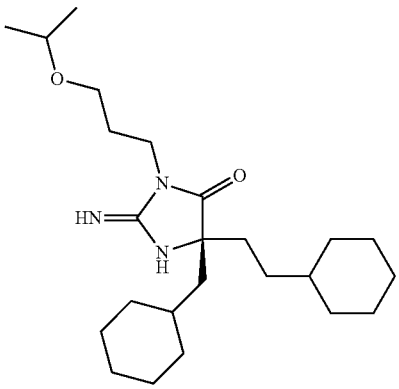
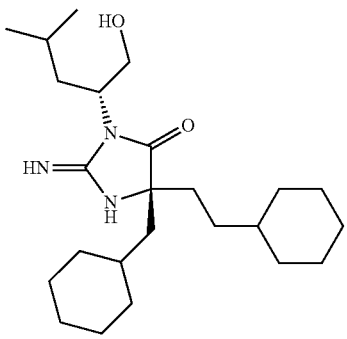
#	Structure	MW	Obs. m/e
121		403	404
122		403	404
123		405	406
124		405	406

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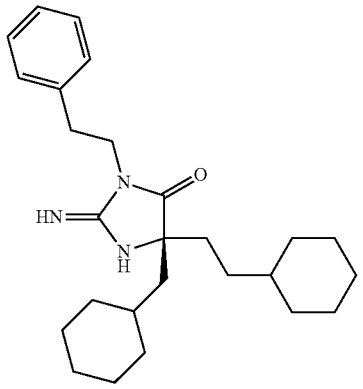
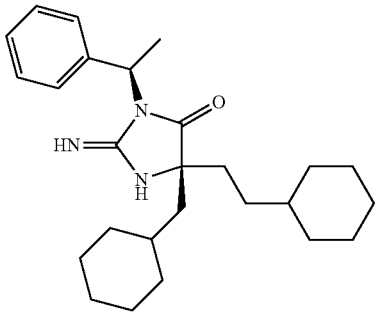
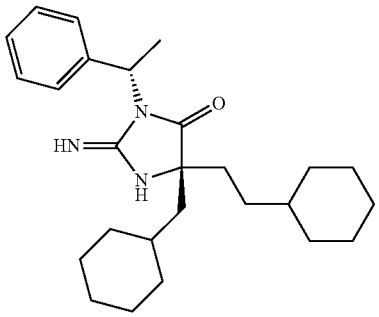
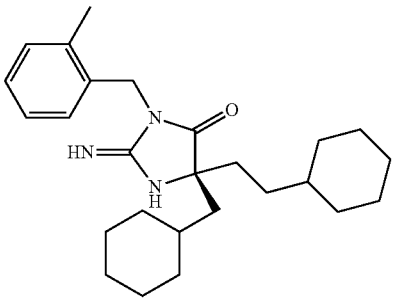
#	Structure	MW	Obs. m/e
125		409	410
126		409	410
127		409	410
128		409	410

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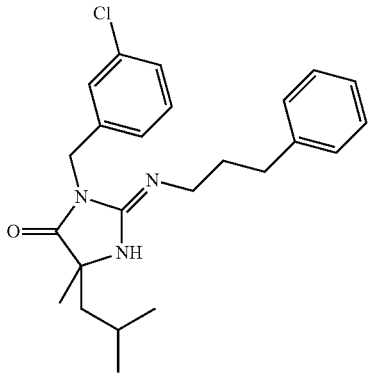
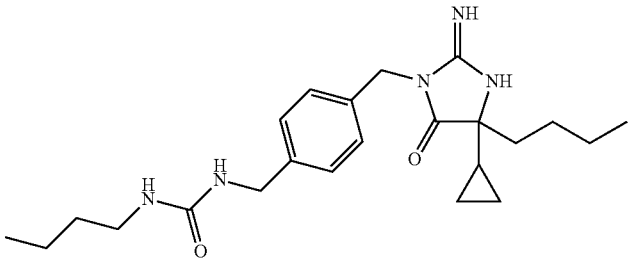
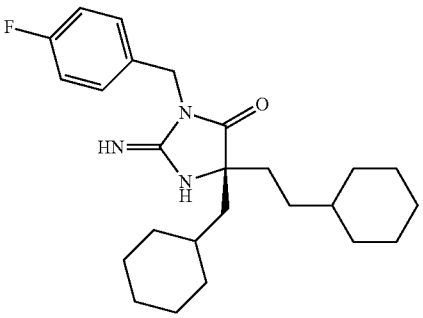
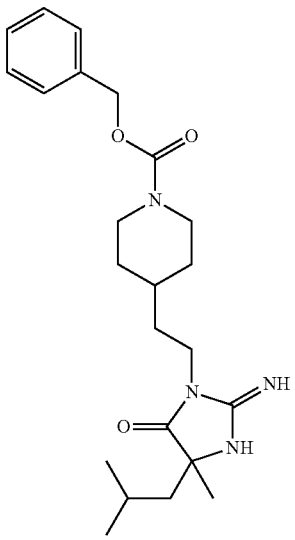
#	Structure	MW	Obs. m/e
129		411	412
130		413	414
131		413	414
132		414	415

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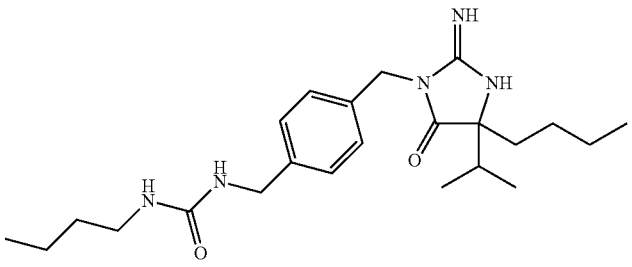
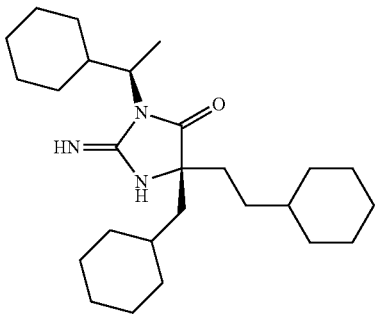
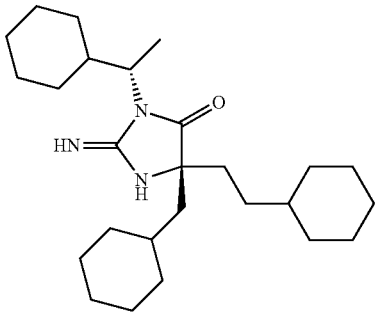
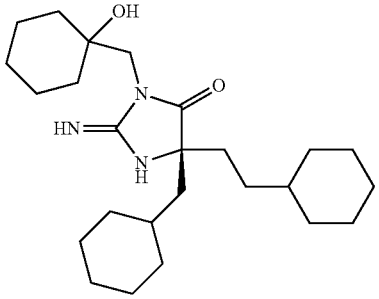
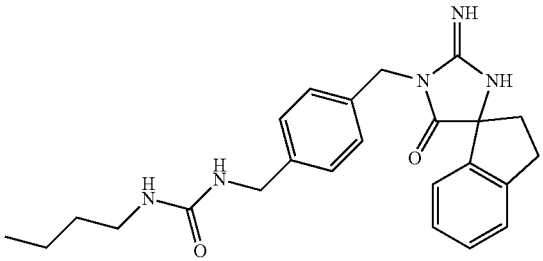
#	Structure	MW	Obs. m/e
133		415	416
134		415	416
135		415	416
136		417	418
137		419	420

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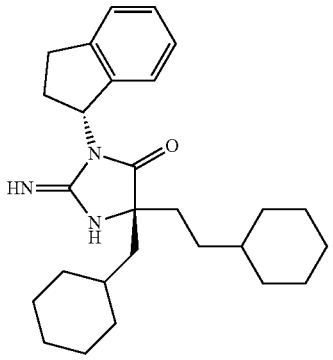
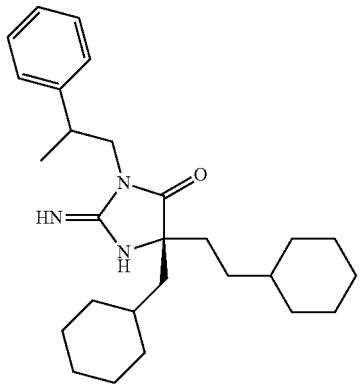
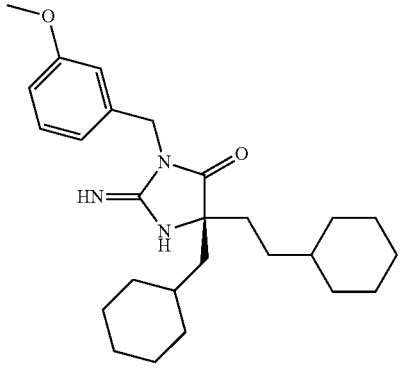
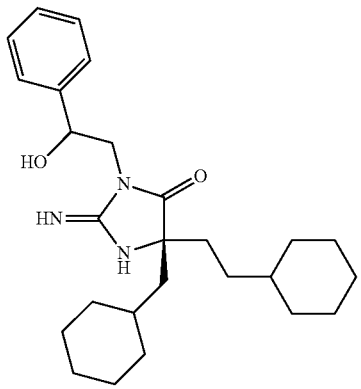
#	Structure	MW	Obs. m/e
138		421	422
139		423	424
140		425	426
141		425	426

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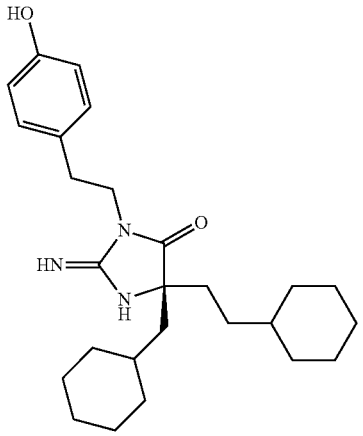
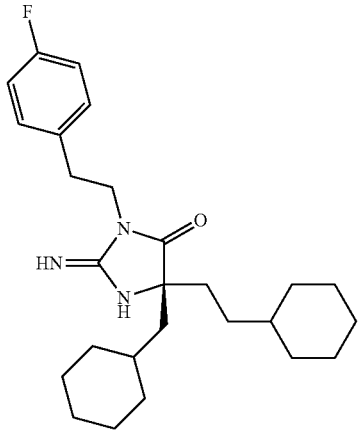
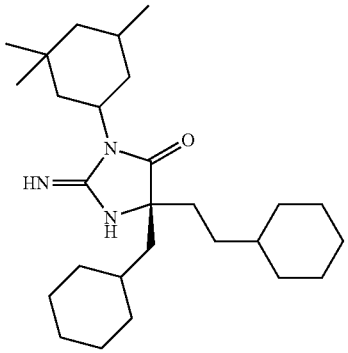
#	Structure	MW	Obs. m/e
142		425	426
143		427	428
144		429	430

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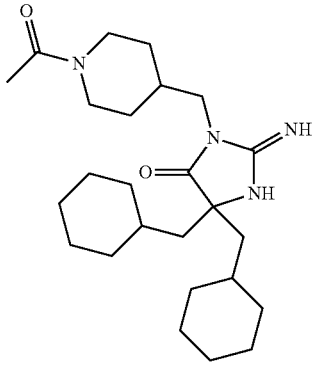
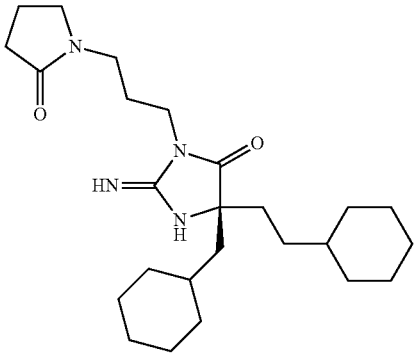
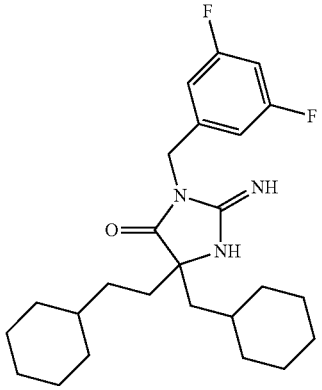
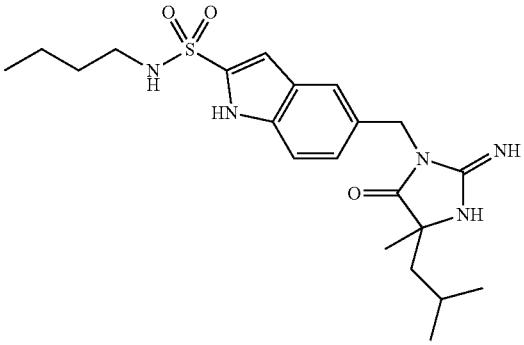
#	Structure	MW	Obs. m/e
145		430	431
146		430	431
147		431	432
148		433	434

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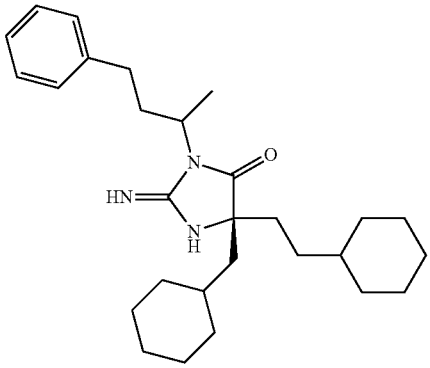
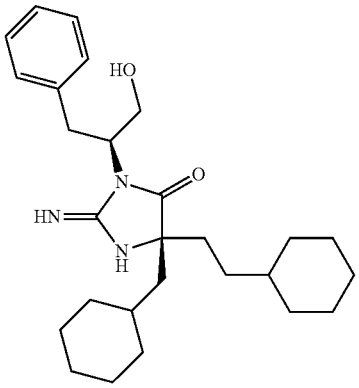
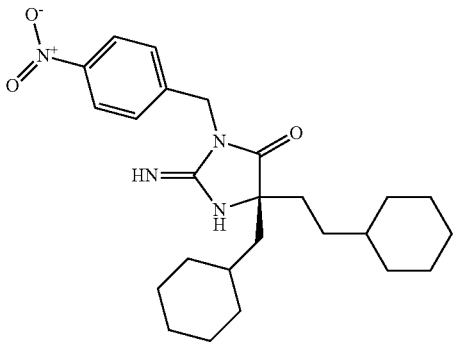
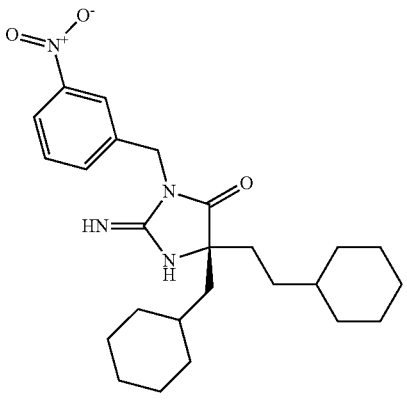
#	Structure	MW	Obs. m/e
149		437	438
150		439	440
151		440	441
152		440	441

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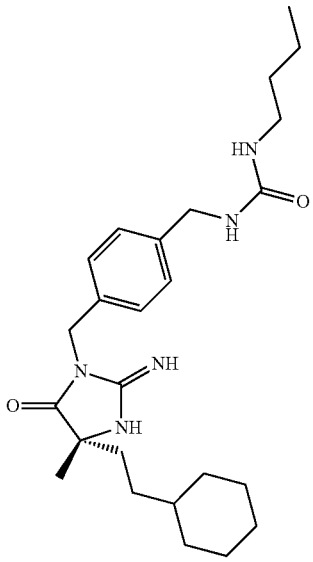
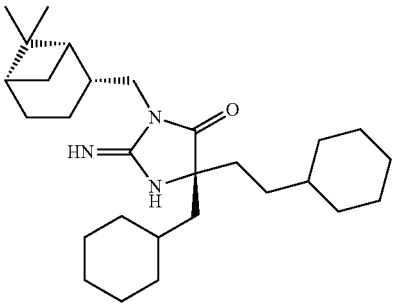
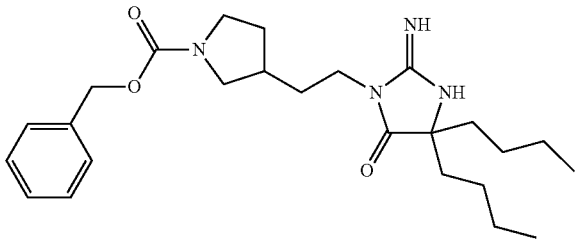
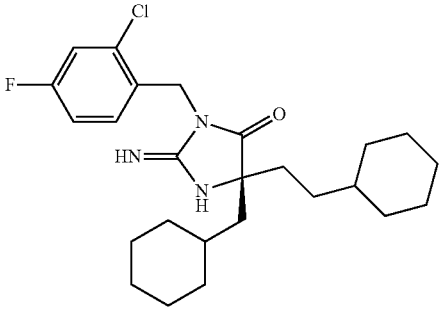
#	Structure	MW	Obs. m/e
153		441	442
154		441	442
155		442	443
156		447	448

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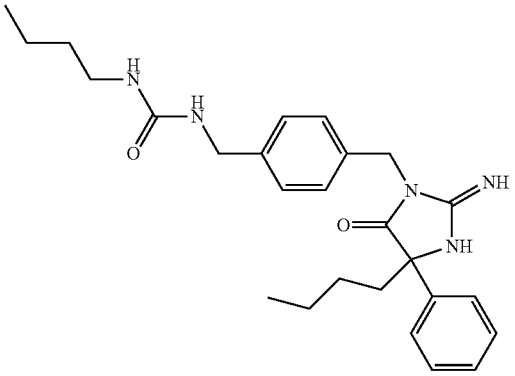
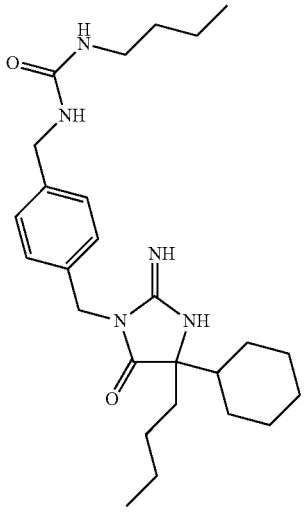
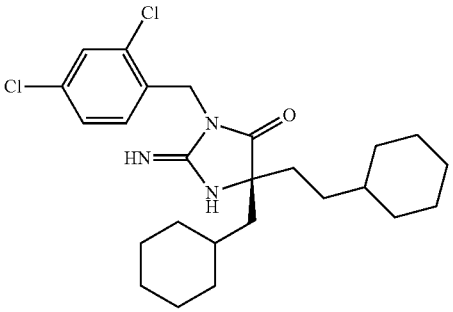
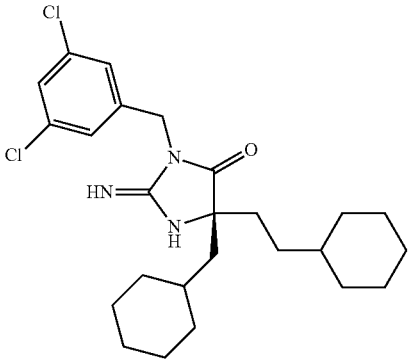
#	Structure	MW	Obs. m/e
157		449	450
158		455	456
159		463	464
160		463	464

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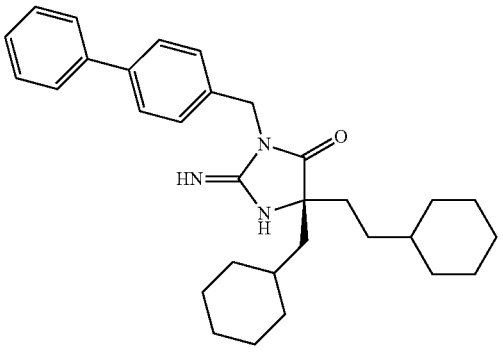
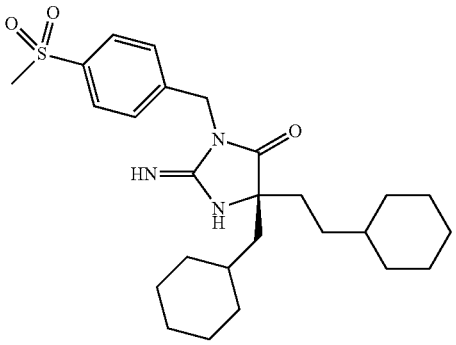
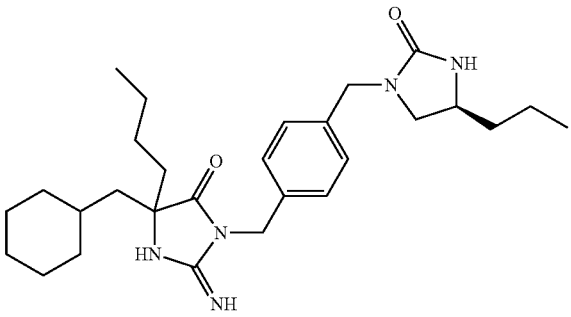
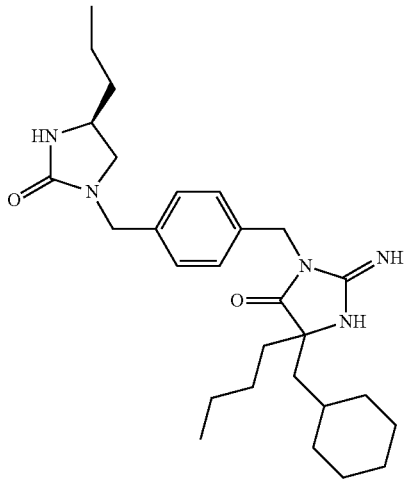
#	Structure	MW	Obs. m/e
161		471	472
162		473	474
163		481	482
164		481	482

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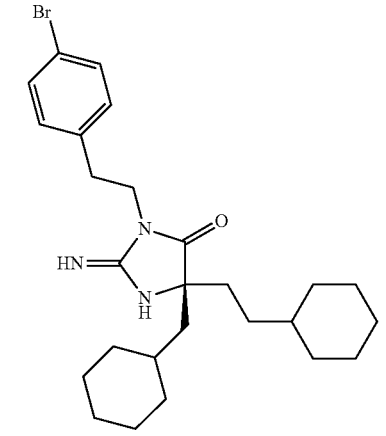
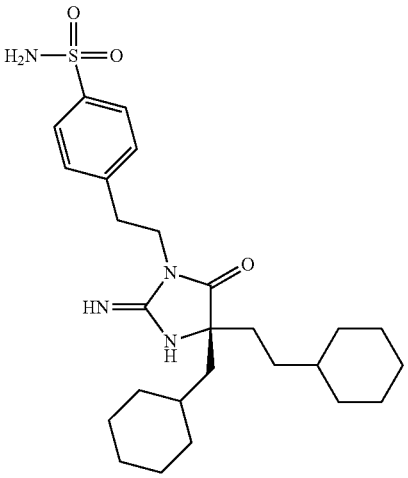
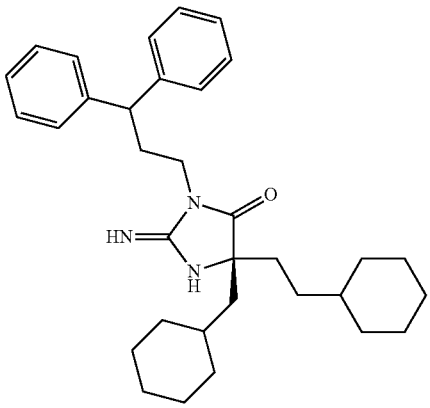
#	Structure	MW	Obs. m/e
165		487	488
166		488	489
167		499	500

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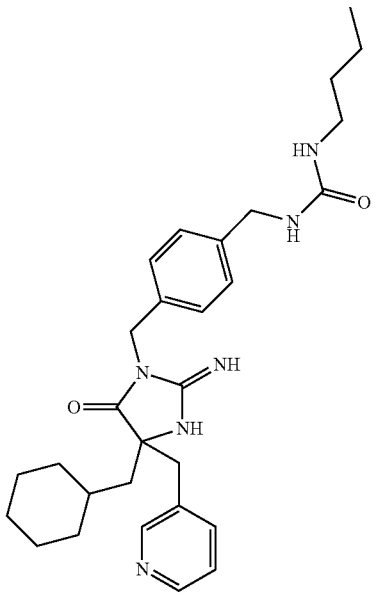
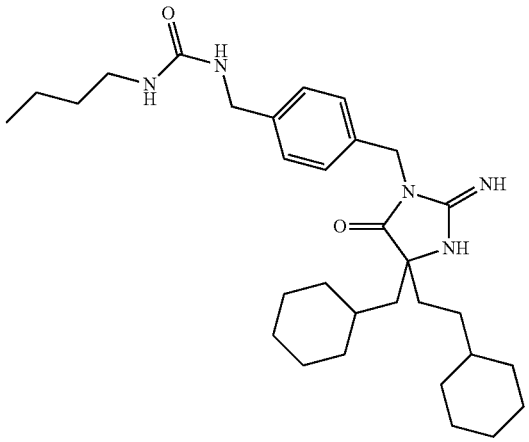
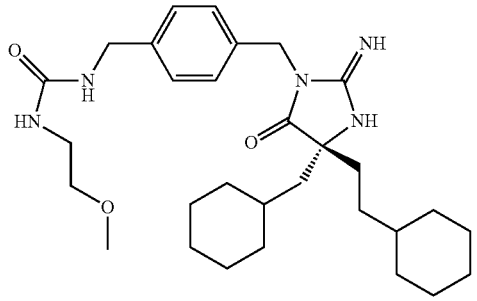
#	Structure	MW	Obs. m/e
168		504	505
169		523	524
170		525	526

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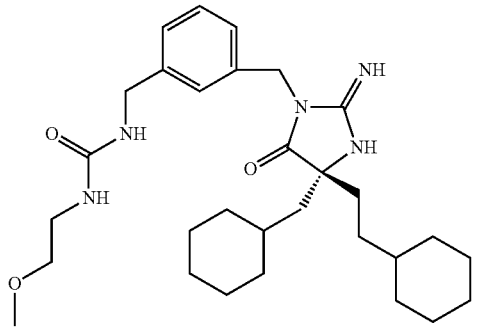
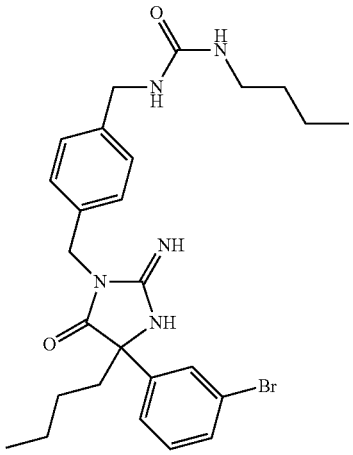
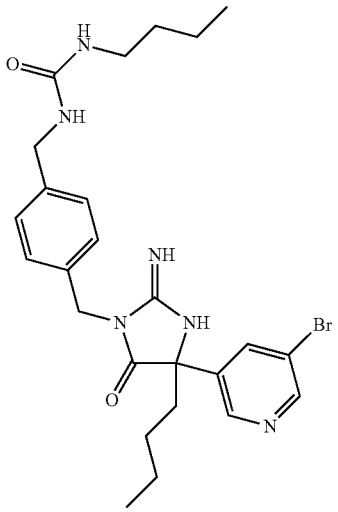
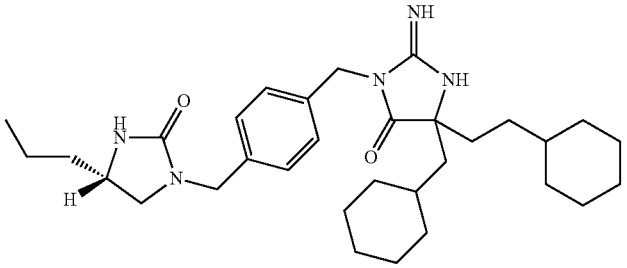
#	Structure	MW	Obs. m/e
171		525	526
172		527	528
173		528	529
174		535	536

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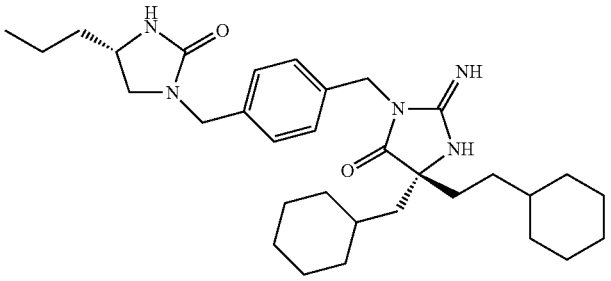
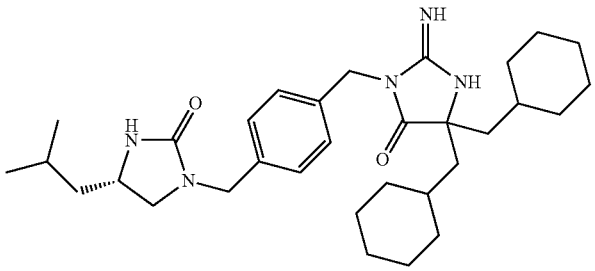
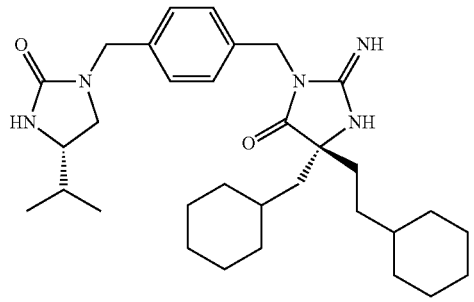
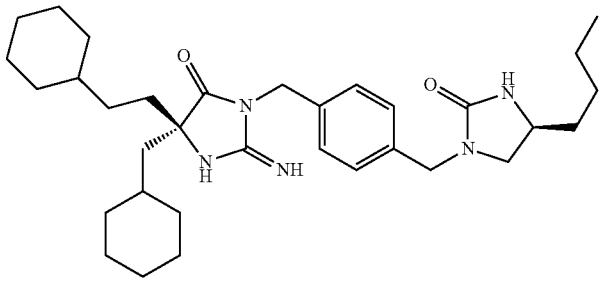
#	Structure	MW	Obs. m/e
175		535	536
176		535	536
177		535	536
178		550	551

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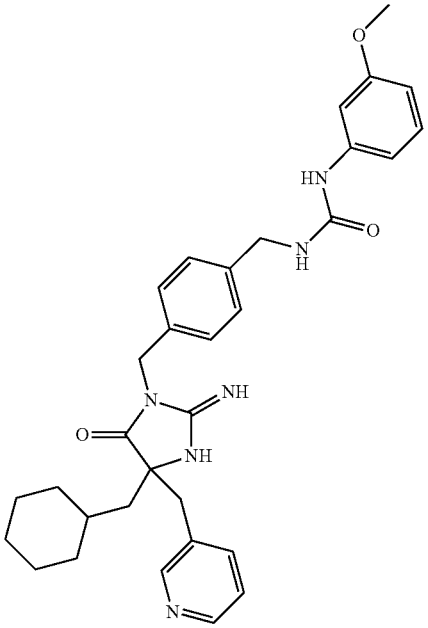
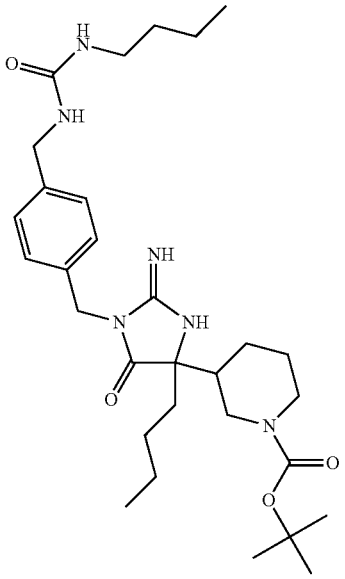
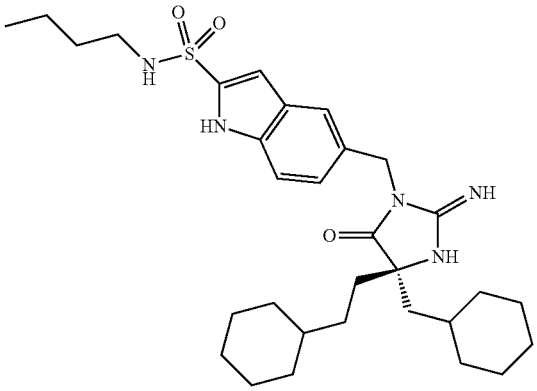
#	Structure	MW	Obs. m/e
179		554	555
180		556	557
181		569	570

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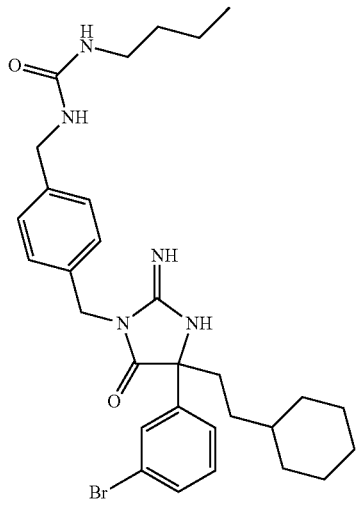
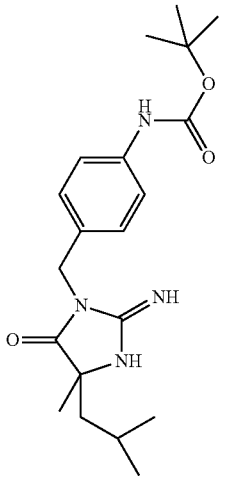
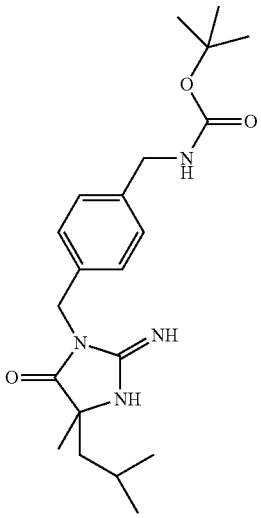
#	Structure	MW	Obs. m/e
182		581	582
183		374	NA
184		388	NA

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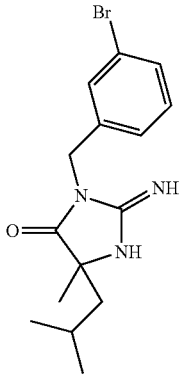
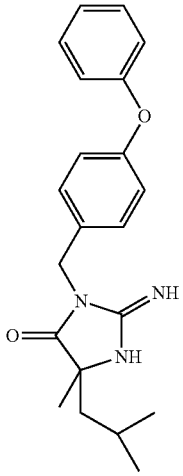
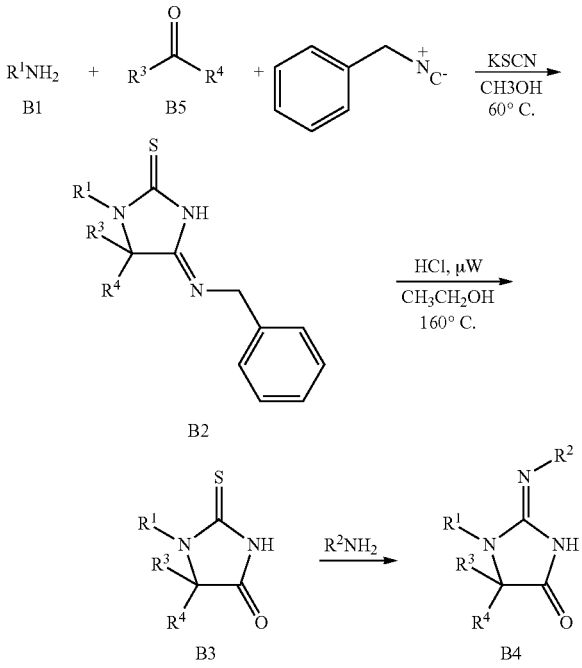
#	Structure	MW	Obs. m/e
185		337	NMR
186		351	NMR

Method B



A modified literature procedure was used (Ugi, I. *Angew. Chem.* 1962, 74 9-22).

Method B, Step 1:

To a solution of B1 (HCl salt, R^1=3-chlorophenethyl) (1.1 g, 5.73 mmol) in anhydrous CH_3OH (15 mL) was added potassium thiocyanate (0.56 g, 5.73 mmol). The reaction mixture was heated to 60° C. for 1 h. The suspension was filtered and the filtrate was added to B5 (R^3=Me, R^4='Bu) (0.72 mL, 5.73 mmol) and benzyl isocyanide (0.77 mL, 6.3 mmol). The mixture was stirred overnight before the solution was concentrated and the residue was purified via flash chromatography eluting with ethyl acetate in hexane to yield 0.28 g of B2 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, and R^1=3-Chlorophenethyl).

Method B, Step 2:

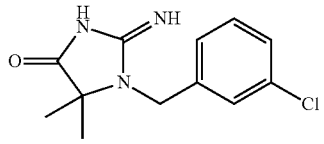
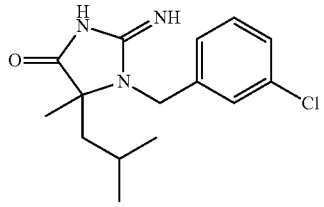
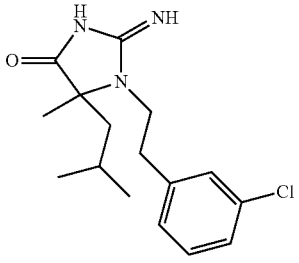
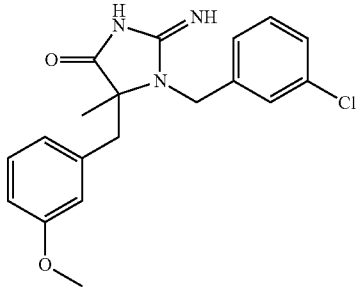
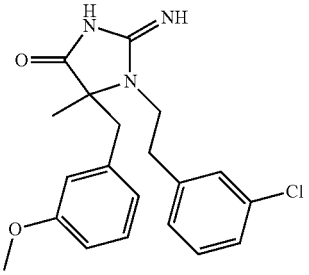
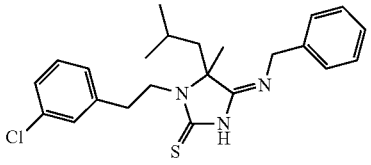
A solution of 40% concentrated HCl in CH_3CH_2OH was added to B2 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, and R^1=3-Chlorophenethyl) and the solution was heated in a microwave at 160° C. for 30 min. The solution was concentrated and purified via reverse phase preparative HPLC eluting with a CH_3CN/H_2O (with 0.1% formic acid) gradient to afford B3 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, and R^1=3-Chlorophenethyl).

Method B, Step 3:

Compound B4 (R^2=H, R_3=CH_3, R^4=$CH_2CH(CH_3)_2$, and R^1=3-Chlorophenethyl) was prepared from B3 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, and R^1=3-Chlorophenethyl) following a procedure similar to Method A, Step 3. NMR(CD_3OD): δ 8.1,

br, 1H; δ 7.35, s, 1H; δ 7.25, m, 3H; δ 3.6, m, 1H; δ 3.4, m, 1H; δ 3.0, m, 1H; δ 2.8, m, 1H; δ 1.75, m, 1H; δ 1.6, m, 1H; δ 1.35, m, 1H; δ 1.2 s, 3H; δ 0.8, m, 6H. ES_LCMS (m/e): 308.1

The following compounds were prepared using similar methods

#	Structure	MW	Obs. m/e
545		251	252
546		293	294
547		307	308
548		357	358
549		371	372
550		413	

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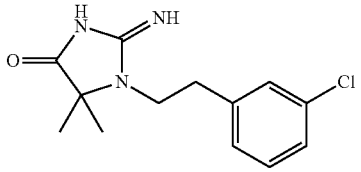
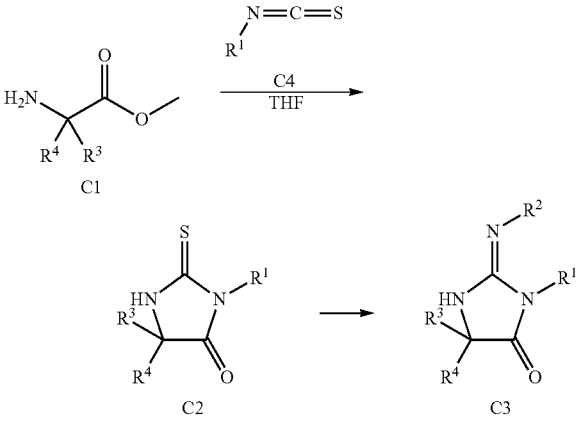
#	Structure	MW	Obs. m/e
551		265	

Method C



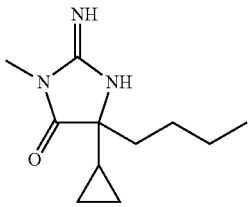
Method C, Step 1:

A solution of C1 (R^3=R^4=$CH_2CH_2CH_2CH_3$) (50 mg, 0.25 mmol) and C4 (R^1=3-chlorophenyl) (38 μL, 0.26 mmol) was refluxed overnight. Trisamine resin (2 eq) and polystyrene isocyanate resin (2 eq) was added and the mixture was agitated. After 3 h, the suspension was filtered and the resin was washed with CH_2Cl_2 (3×) and CH_3OH (3×). The filtrate was concentrated to afford C2 (R^1=3-Cl—C_6H_4, R^3=R^4=$CH_2CH_2CH_2CH_3$) (60 mg, 68%).

Method C, Step 2

Compound C3 (R^1=3-Cl—C_6H_4, R^2=H, R^3=R^4=$CH_2CH_2CH_2CH_3$) was prepared from C2 (R^1=3-Cl—C_6H_4, R^3=R^4=$CH_2CH_2CH_2CH_3$) following a procedure similar to Method A, Step 3. NMR(CDCl3): δ 7.4, m, 2H; δ 7.2, m, 2H; δ 5.0, s, 2H; δ 1.7, m, 4H; δ 1.1, m, 8H; δ 0.7; m, 6H. ES-LCMS (m/e): 336.1.

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e
641		209	210

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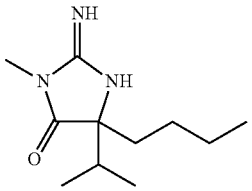
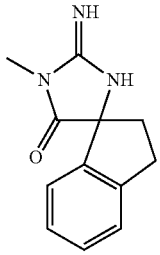
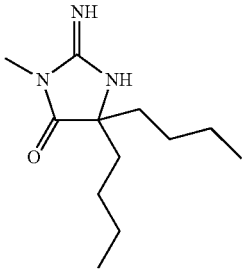
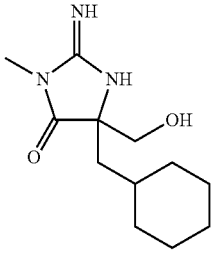
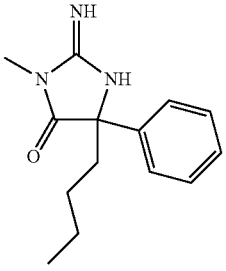
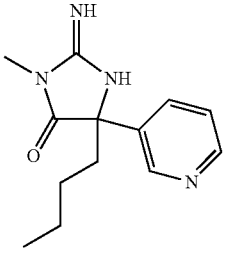
#	Structure	MW	Obs. m/e
642		211	212
643		215	216
644		225	226
645		239	240
646		245	246
647		246	247

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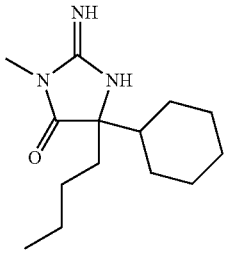
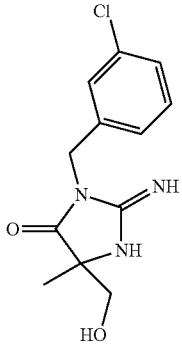
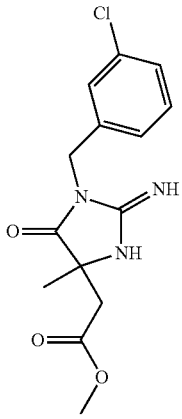
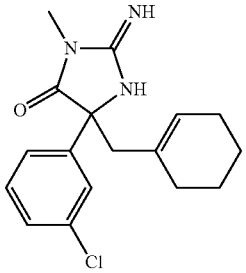
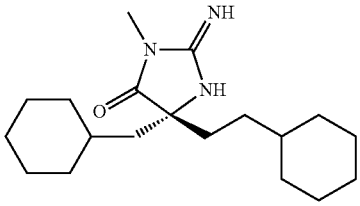
648		251	252
649		267	268
650		309	310
651		317	318
652		319	320

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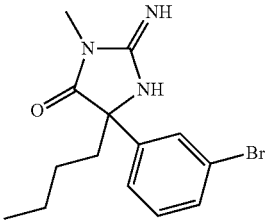
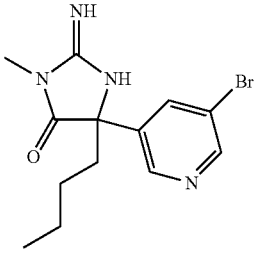
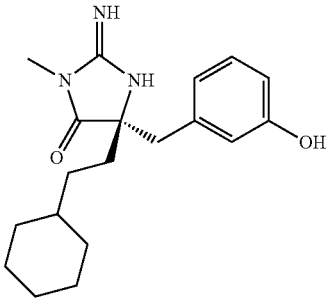
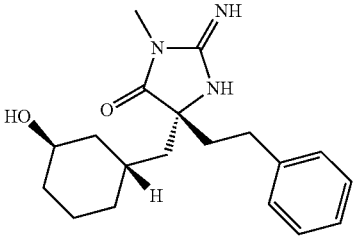
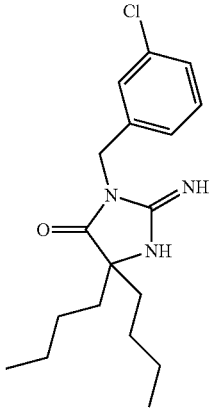
653		323	324
654		324	325
655		329	330
656		329	330
657		335	336

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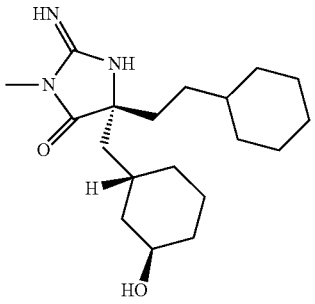
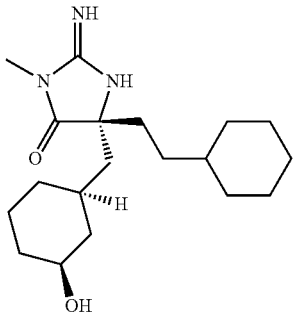
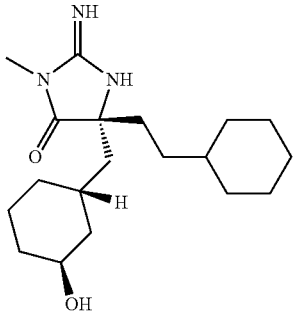
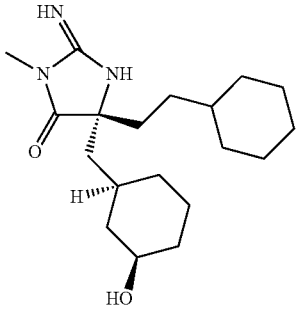
658		335	336
659		335	336
660		335	336
661		335	336

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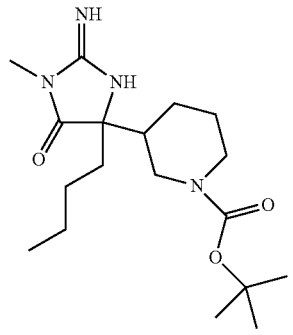
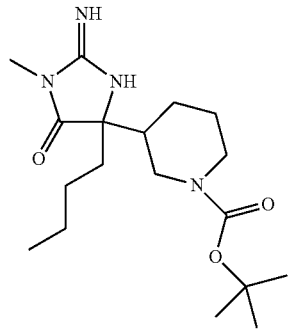
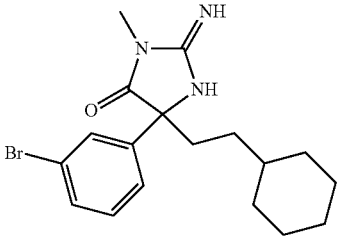
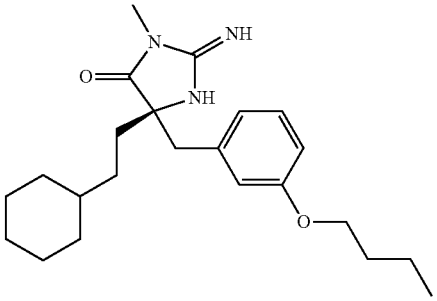
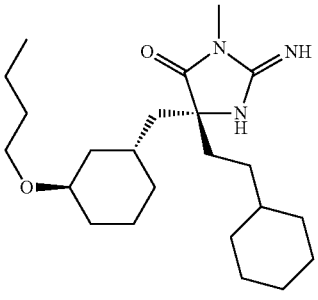
662		352	353
663		352	353
664		377	378
665		385	386
666		391	392

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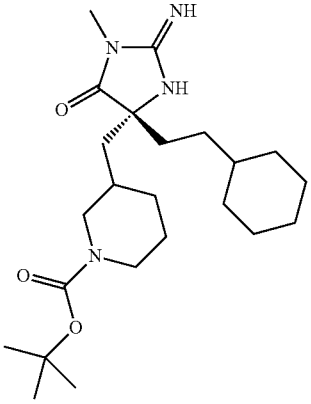
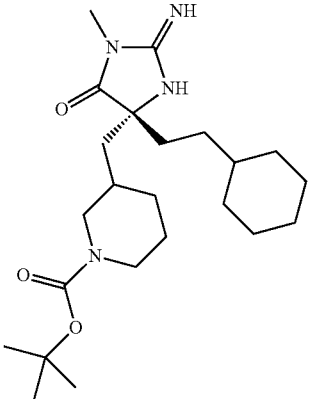
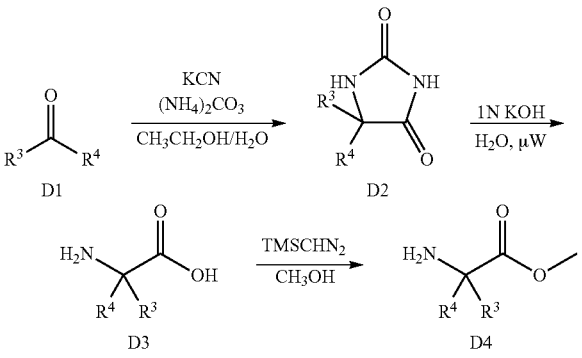
667		420	421
668		420	421

Method D



Method D, Step 1:

A mixture of D1 (R^3=R^4=$CH_2C_6H_5$) (20 g), potassium cyanide (40 g) and ammonium carbonate (15 g) in ethanol (100 mL) and H_2O (200 mL) was heated in a sealed flask at 130° C. overnight to yield 25 g of D2 (R^3=R^4=$CH_2C_6H_5$) after filtration followed by washing with water.

Method D, Step 2:

A solution of 2 N KOH (3 eq) was added to D2 (R^3=R^4=$CH_2C_6H_5$) (1 eq) and irradiated via microwave at 185° C. for 3 h followed by addition of concentrated HCl to

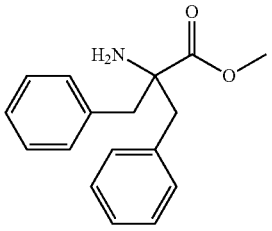
the solution until a pH=2-3 was obtained. The solid was filtered and washed with water to afford D3 (R^3=R^4=$CH_2C_6H_5$).

Method D, Step 3:

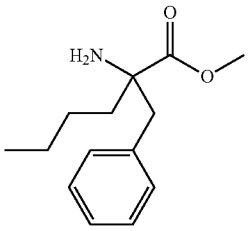
A solution of trimethylsilyldiazomethane in hexane (2 N) (2 eq) was added drop wise to a solution of D3 (R^3=R^4=$CH_2C_6H_5$) (1 eq) in anhydrous CH_3OH (30 mL). After 1 h, an additional 2 eq of trimethylsilyldiazomethane in hexane (2 N) was added and the reaction was stirred for 20 minutes before it was was concentrated. The residue was dissolved in a 0.2 N HCl solution (25 mL) and washed with ether (3×). A saturated solution of Na_2CO_3 was added to the aqueous phase until the pH of the solution was basic. The solution was extracted with ethyl acetate (3×). The organic extracts were combined, dried over Na_2SO_4, and concentrated to afford D4 (R^3=R^4=$CH_2C_6H_5$).

The following amino esters were prepared using a similar method.

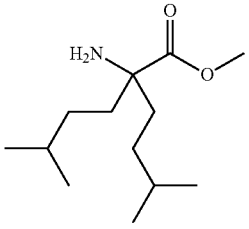
D5



D6



D7



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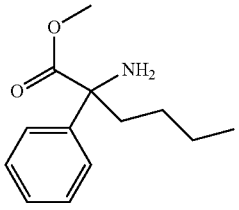

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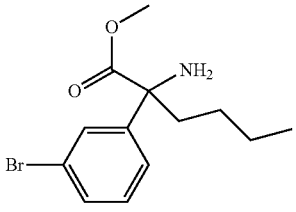

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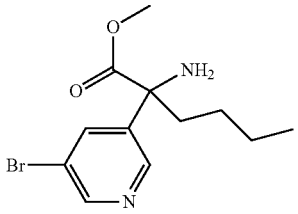
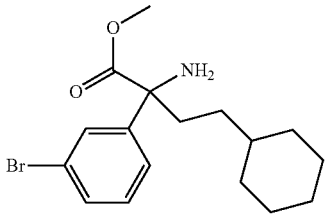
D10



D11



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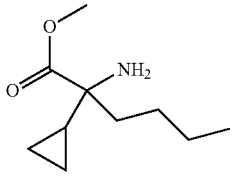

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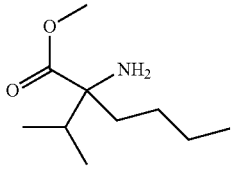
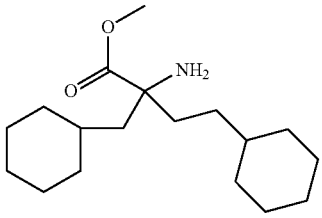
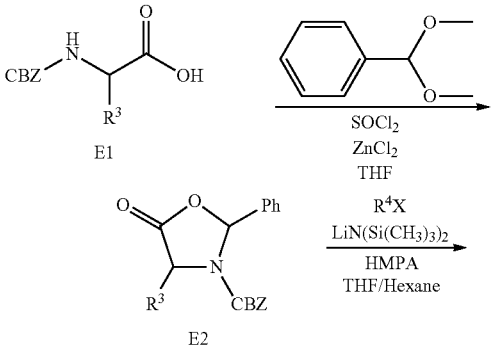


D14



Method E



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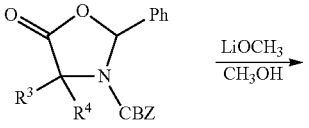
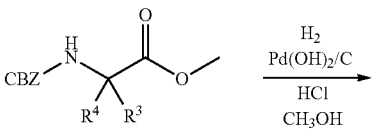
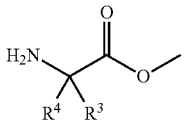


E3



E4



E5

Method E, Step 1:

Thionyl chloride (0.47, 6.38 mmol) was added drop wise to a solution of E1 (R^3=$CH_2CH_2C_6H_5$) (2 g, 6.38 mmol) and benzaldehyde dimethyl acetal (0.96 mL, 6.38 mmol) in anhydrous THF at 0° C. under N_2. After 5 min, $ZnCl_2$ (0.87 g, 6.38 mmol) was added and the reaction mixture was stirred at 0° C. After 3 h, an additional amount of $ZnCl_2$ (0.18 g, 1.28 mmol) and thionyl chloride (0.1 mL, 1.28 mmol) were added and stirred for 1 h at 0° C. The reaction mixture was poured into a stirred suspension of ice/H_2O. The mixture was stirred occasionally until the ice melted. The aqueous solution was extracted with ether (3×). The combined organic extracts were washed with H_2O (3×), a sat. aqueous solution of $NaHCO_3$ (1×), and H_2O (2×). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to yield compound E2 (R^3=$CH_2CH_2C_6H_5$).

Method E, Step 2:

A solution of lithium hexamethyldisilazide in hexane (1.0 M, 1.65 mL, 1.64 mmol) was added drop wise to a solution of E2 (R^3=$CH_2CH_2C_6H_5$) (600 mg, 1.49 mmol) and HMPA (0.85 mL) in THF (6.5 mL) cooled at −78° C. under N_2. After 15 min, isobutyl iodide (0.52 mL, 4.48 mmol) was added drop wise and the reaction mixture was stirred at −78° C. for 3 h. The reaction was warmed to −65° C., stirred for 2 h and warmed to rt overnight. The reaction solution was poured into a mixture of sat. $NaHCO_3$ (aq)/ether/ice. The aqueous layer was extracted with ether (3×). The organic extracts were combined and washed with brine (2×). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to yield compound E3 (R^3=$CH_2CH_2C_6H_5$, R^4=$CH_2CH(CH_3)_2$).

Method E, Step 3:

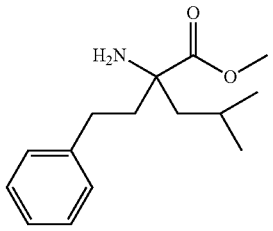
A solution of lithium methoxide (1 N in CH_3OH) (0.36 mL, 0.36 mmol) was added to compound E3 (R^3=$CH_2CH_2C_6H_5$, R^4=$CH_2CH(CH_3)_2$). The reaction mixture was shaken at rt for 50 min. An additional 0.55 eq of lithium methoxide were added. After 2.5 h, a sat. aqueous solution of $NaHSO_3$ (0.75 mL) and ethyl acetate (3 mL) was added to the reaction mixture and shaken for 15 min. The suspension was filtered. The resulting white solid was washed with a sat. aqueous solution of $NaHSO_3$ (1×) and ethyl acetate (1×). The aqueous phase of the filtrate was separated and extracted with ethyl acetate (2×). The organic extracts were combined and washed with a sat. aqueous solution of $NaHSO_3$ (8×). The organic solution was dried over Na_2SO_4, filtered and concentrated to afford E4 (R^3=$CH_2CH_2C_6H_5$, R^4=$CH_2CH(CH_3)_2$) (109 mg, 87%).

Method E, Step 4:

To a solution of E4 (R^3=$CH_2CH_2C_6H_5$, R^4=$CH_2CH(CH_3)_2$) (109 mg, 0.28 mmol) in CH_3OH (4 mL) was added 1 N HCl (0.28 mL, 0.28 mmol) and 20% palladium hydroxide on carbon (22 mg). The reaction mixture was hydrogenated at 40 psi. After 2.5 h, the reaction was filtered and the catalyst was washed with CH_3OH (3×). The filtrate was concentrated to afford E5 (R^3=$CH_2CH_2C_6H_5$, $R^4CH_2CH(CH_3)_2$) (78 mg, 96%).

The following aminoesters were prepared using similar method.

E6



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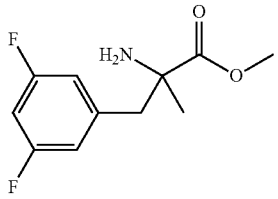

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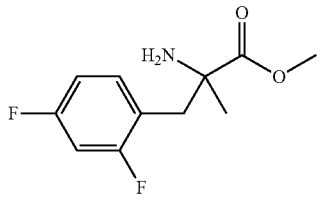

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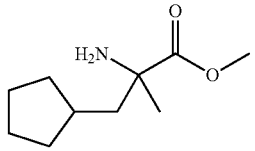

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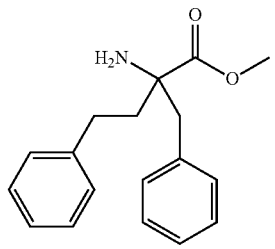

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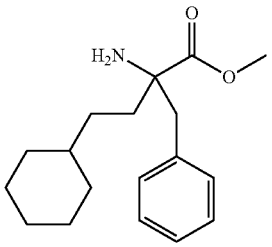

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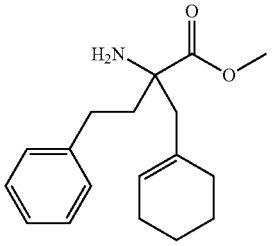

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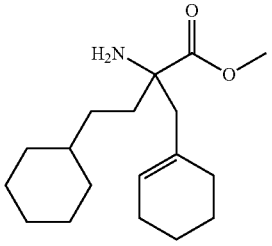

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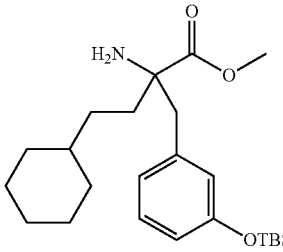

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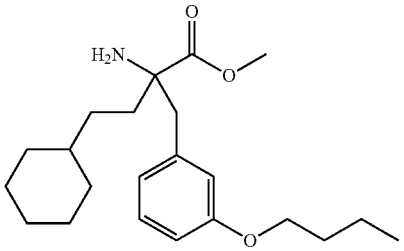

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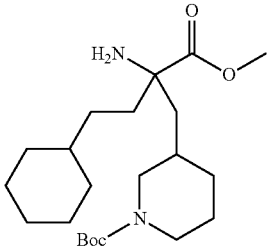

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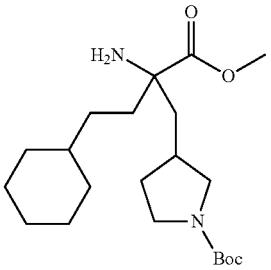

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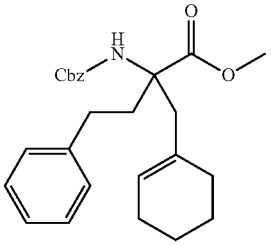

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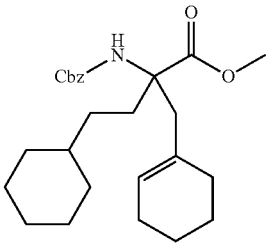
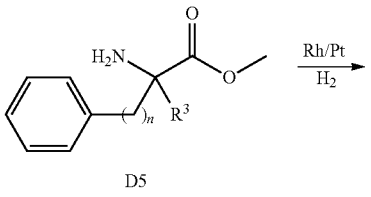
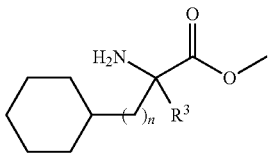


Method F



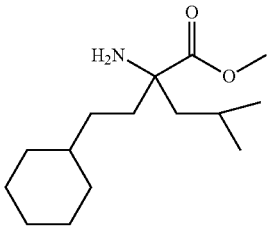
D5

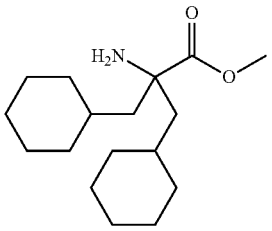


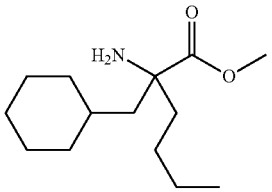
F1

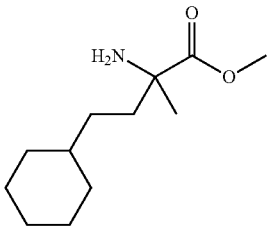
A 500 mL methanol solution of 20 g of D5 (R^3=benzyl, n=1) with 1.5 eq of HCl was hydrogenated with 1 g of Rh/C (5% w/w) and 2 g of Pt/C (5% w/w) at 60 psi for 2 days. The solid was filtered and washed with excessive methanol. The combined solution was evaporated to give 20 g of F1 (R^3=cyclohexylmethyl, n=1) as HCl salt.

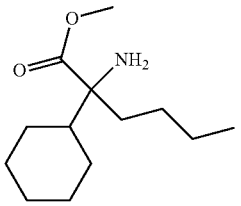
The following amino esters were examples prepared using similar method.

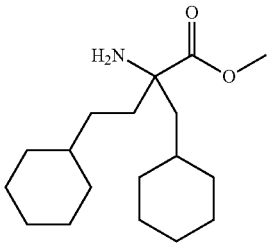


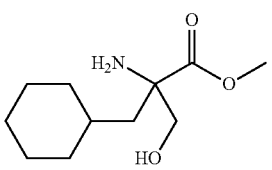












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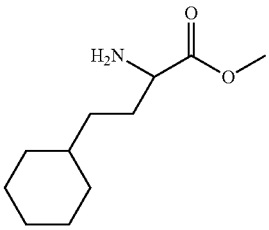
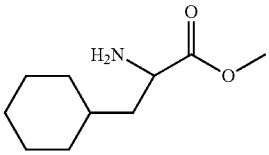
F2



F9

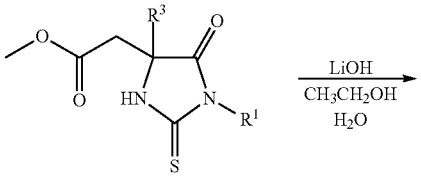
F3



F10

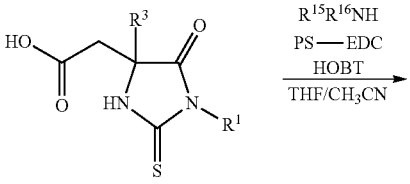
Method G

F4



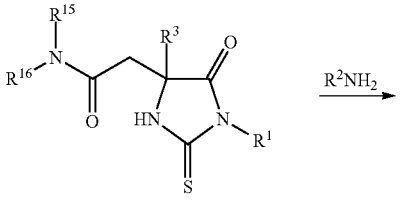
G1

F5



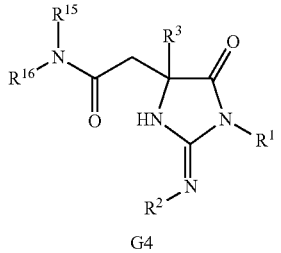
G2

F6



G3

F7



G4

F8

Method G, Step 1:

To a solution of G1 (R^1=CH_2(3-ClC_6H_4) and R^3=CH_3) (400 mg, 1.23 mmol, generated following a procedure similar to Method C, Step 1) in ethanol (5 mL) was added lithium hydroxide monohydrate (100 mg, 2.45 mmol) in H_2O (0.5 mL). After 2.5 h, another portion of lithium hydroxide monohydrate (100 mg, 2.45 mmol) was added. After 5.5 h, the

reaction mixture was diluted with H_2O (15 mL) and extracted with ether (2×). A solution of 30% HCl was added to the aqueous phase until its pH=1 to 2. The solution was saturated with NaCl and extracted with ethyl acetate (3×). The organic solution was dried over Na_2SO_4, filtered and concentrated to afford G2 (R^1=CH_2(3-ClC_6H_4) and R^3=CH_3) (357 mg, 93%).

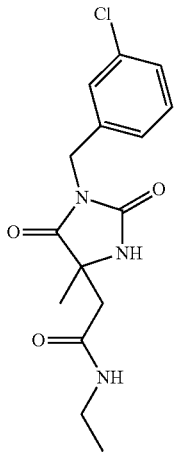
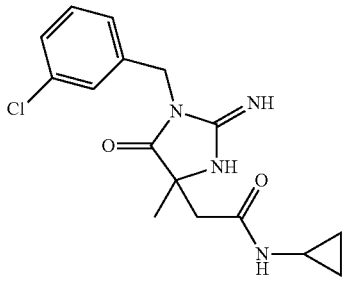
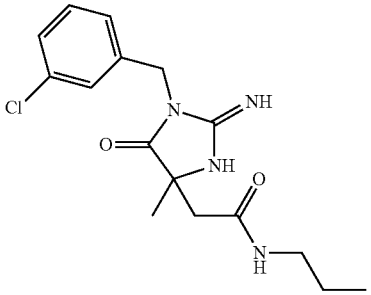
Method G, Step 2:

A solution of benzyl amine (1.2 eq) was added to G2 (R^1=CH_2(3-ClC_6H_4) and R^3=CH_3) (1 eq), HOBT (1.5 eq) and polystyrene EDC resin (94 mg, 1.53 mmol/g, 3 eq) in 1:1 THF:CH_3CN (1 mL). The reaction mixture was shaken overnight at rt. Trisamine resin (85 mg, 3.38 mmol/g, 6 eq) and isocyanate resin (100 mg, 1.47 mmol/g, 3 eq) was added. After 6 h, the suspension was filtered and the filtrate was concentrated to afford G3 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, R^{15}=$CH_2C_6H_5$ and R^{16}=H).

Method G, Step 3:

Compound G4 (R^1=CH_2(3-ClC_6H_4), R^2=H, R_3=CH_3, R^{15}=$CH_2C_6H_5$ and R^{15}=H) was prepared from G3 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, R^{15}=$CH_2C_6H_5$ and R^{16}=H) following a procedure similar to Method A, Step 3.

The following compounds were prepared using similar methods.

#	Structure	MW	Obs. m/e
669		322	323
670		334	335
671		336	337

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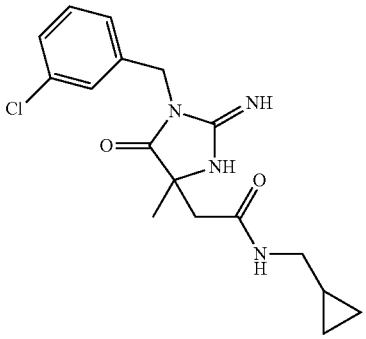
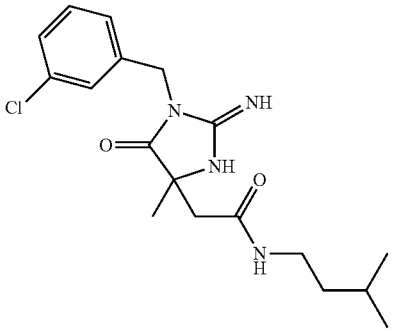
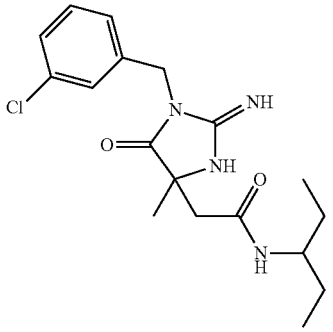
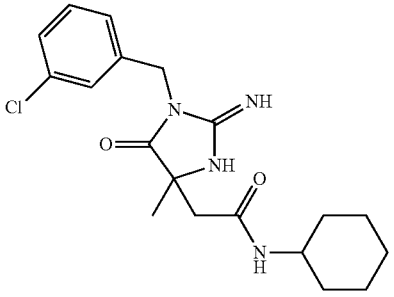
#	Structure	MW	Obs. m/e
672		348	349
673		364	365
674		364	365
675		376	377

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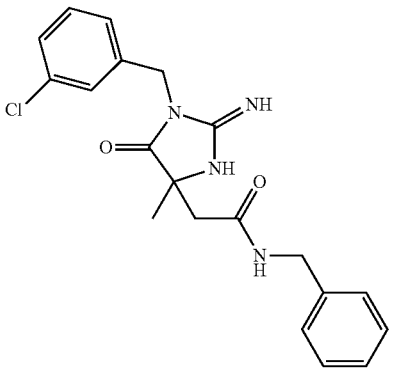
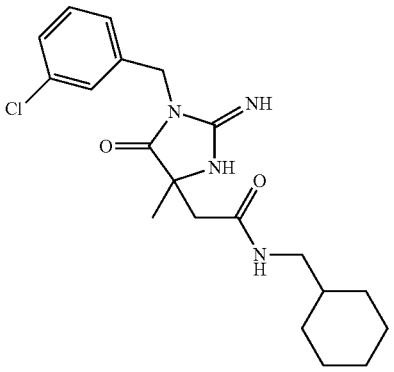
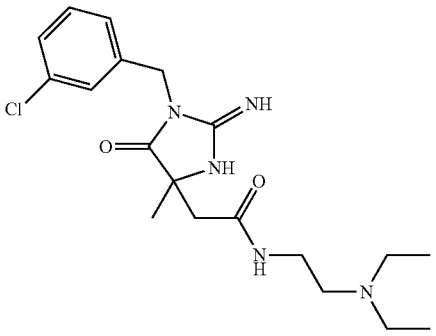
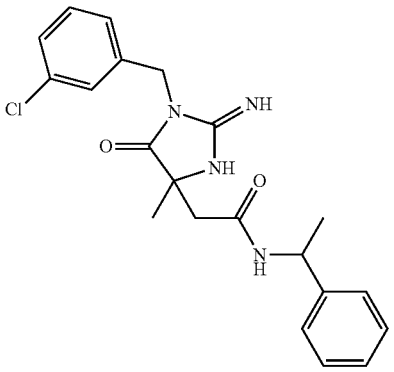
#	Structure	MW	Obs. m/e
676		384	385
677		390	391
678		393	394
679		398	399

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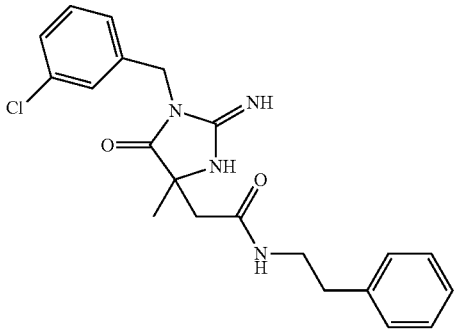
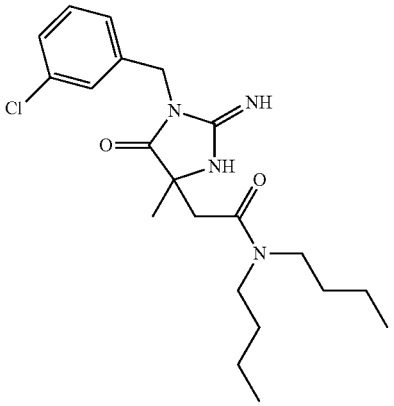
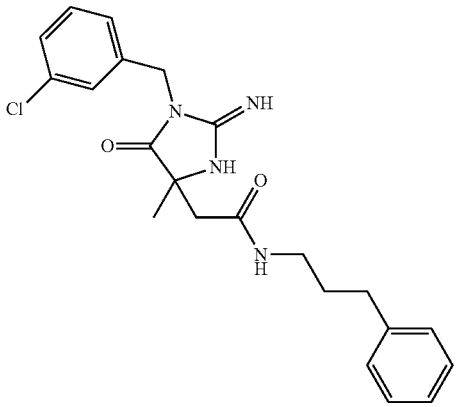
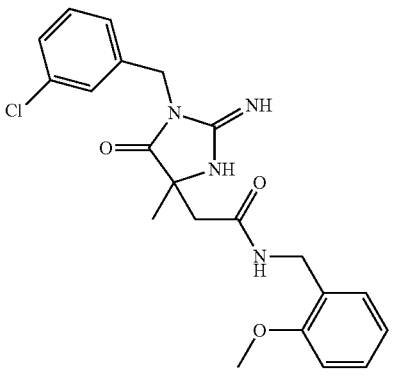
#	Structure	MW	Obs. m/e
680		398	399
681		406	407
682		412	413
683		414	415

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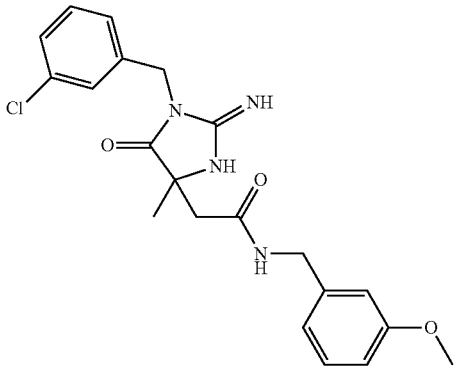
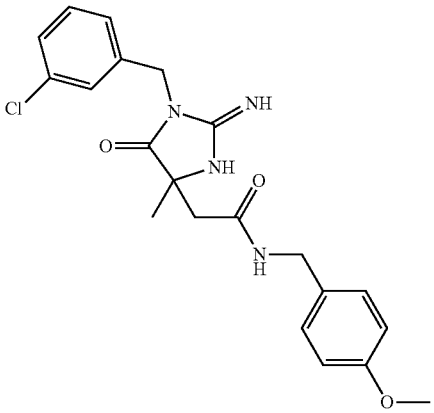
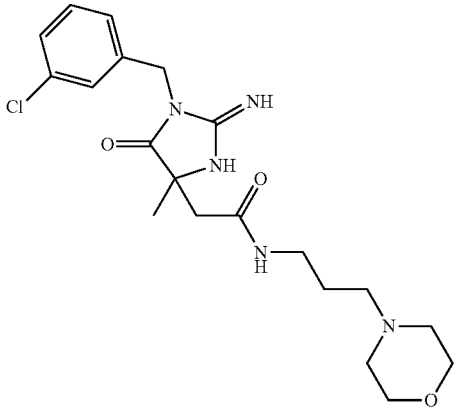
#	Structure	MW	Obs. m/e
684		414	415
685		414	415
686		421	422

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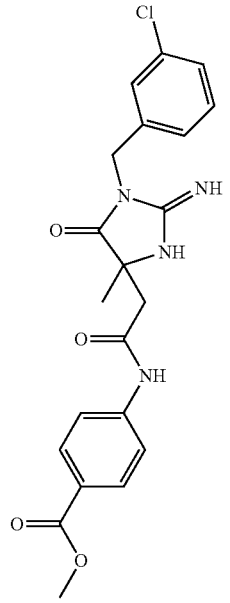
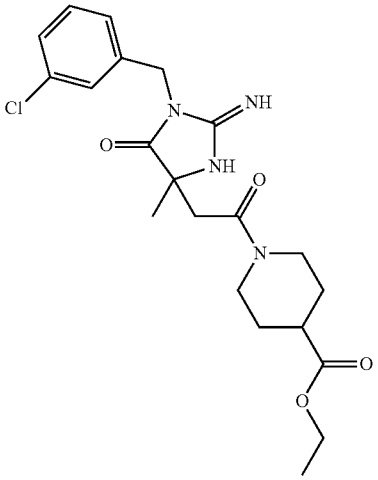
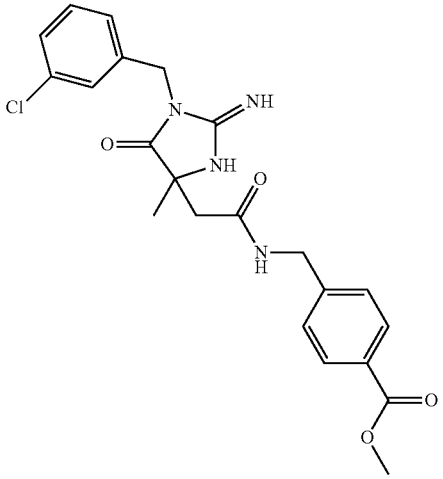
687		428	429
688		434	435
689		442	443

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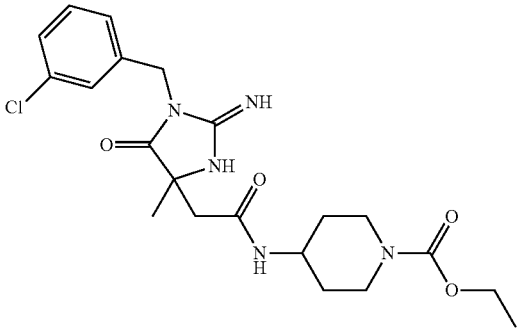
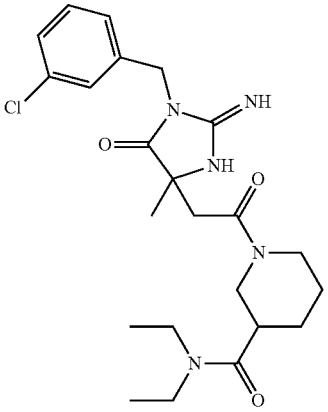
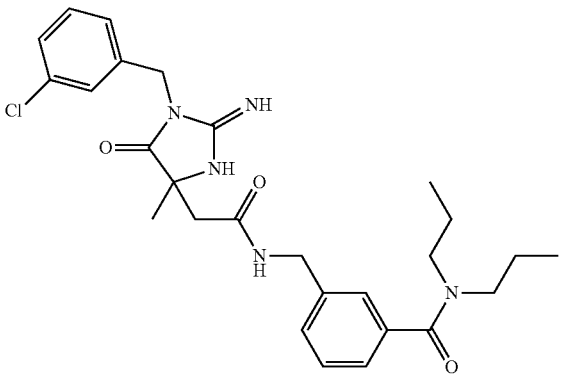
690		449	450
691		461	462
692		511	512

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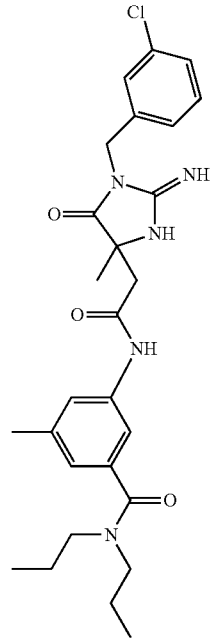
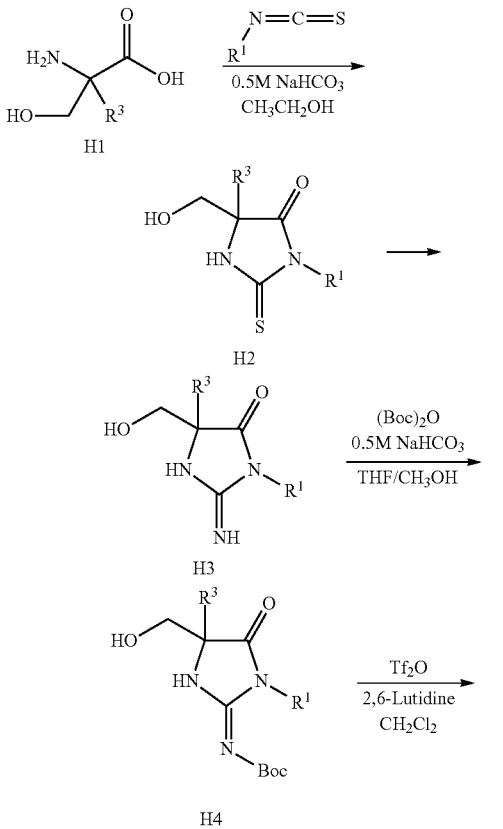
693		511	512

Method H



H1 H2 H3 H4

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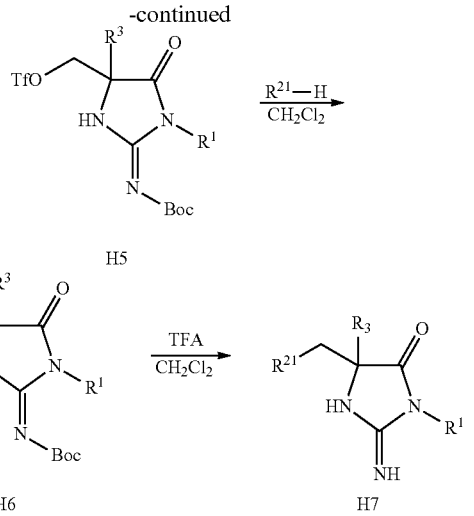

H5 H6 H7

Method H, Step 1:

To a solution of H1 (R^3=CH_3) (5 g, 39 mmol) in a 1:1 mixture of 0.5 M $NaHCO_3$:CH_3CH_2OH was added R^1—NCS (R^1=3-chlorobenzyl) (11.5 mL, 78 mmol). The reaction mixture was heated at 50° C. overnight. The reaction was cooled and diluted with water. The aqueous phase was extracted with ethyl acetate (5×). The organic extracts were combined, washed with water (2×) and dried over Na_2SO_4. The solution was filtered and solvent was removed to give a small volume of solution. Hexane was added and the resulting suspension was filtered to yield 6.8 g of a solid H2 (R^3=CH_3, R^1=CH_2(3-ClC_6H_4)) (61%).

Method H, Step 2:

Compound H3 (R^3=CH_3, R^1=CH_2(3-ClC_6H_4)) was synthesized from H2 (R^3=CH_3, R^1=CH_2(3-ClC_6H_4)) following a procedure similar to Method A, Step 3.

Method H, Step 3:

To a solution of crude H3 (R^3=CH_3, R^1=CH_2(3-ClC_6H_4)) (14 mmol) in a 1:3 mixture of CH_3OH:THF was added 0.5 M $NaHCO_3$ in H_2O (28 mL, 14 mmol) and di-tert-butyl dicarbonate (3.69 g, 16.9 mmol). The reaction was stirred at rt for 2.5 h and then stored at −10° C. overnight. The reaction was diluted with brine and extracted with ethyl acetate (4×). The organic extracts were combined and washed with brine (1×). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography eluting with ethyl acetate in hexane to afford 1.5 g of H4 (R^1=CH_2(3-ClC_6H_4) and R^3=CH_3).

Method H, Step 4:

A solution of triflic anhydride (128 μL, 0.76 mmol) in CH_2Cl_2 (5 mL) was added drop wise to a solution of H4 (R^1=CH_2(3-ClC_6H_4) and R^3=CH_3) (200 mg, 0.55 mmol) and 2,6-lutidine (176 μL, 2.18 mmol) at −30° C. The reaction mixture was stirred for 1.5 h. Water (10 mL) was added at −20° C. and the ice bath was removed. The reaction was stirred until it reached 0° C. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to afford 310 mg of H5 (R^1=CH_2(3-ClC_6H_4) and R^3=CH_3).

Method H, Step 5:

A solution of crude H5 (R^1=CH_2(3-ClC_6H_4) and R^3=CH_3) (0.11 mmol) and 7N ammonia in Methanol (R^{21}—H=NH_2—H) (10 eq) was stirred overnight at rt. The reaction solution was concentrated. The crude material was purified using reverse phase preparative HPLC eluting with a CH_3CN/H_2O gradient with 0.1% formic acid to yield H6=CH_2(3-ClC_6H_4), R^3=CH_3, R^{21}=NH_2).

Method H, Step 6:

A solution of 50% trifluoroacetic acid in CH_2Cl_2 (2 mL) was added to H6 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, R^{21}=NH_2). After 40 min the solvent was evaporated and residue purified by preparative HPLC/LCMS eluting with a CH_3CN/H_2O gradient to afford H7 (R^1=CH_2(3-ClC_6H_4), R_3=CH_3, R^{21}=NH2). NMR ($CDCl_3$), δ 7.45, m, 3H; δ 7.35, m, 1H; δ 4.9, m, 2H; δ 3.5, m, 2H; δ 1.65, s, 3H. ES_LCMS (m/e) 267.07.

The following compounds were prepared using similar methods.

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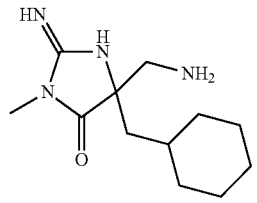
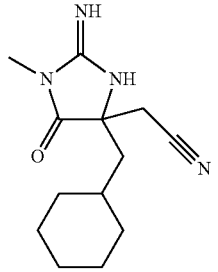
694		238	239
695		248	249

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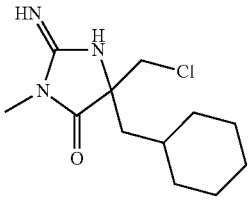
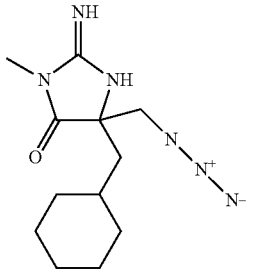
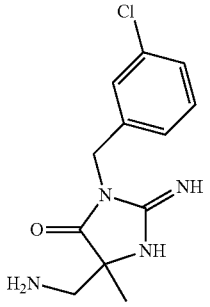
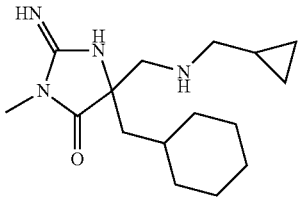
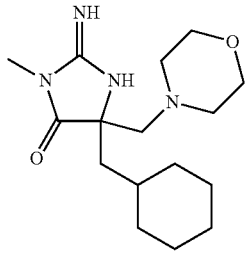
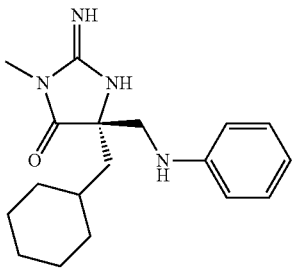
696		257	258
697		264	265
698		266	267
699		292	293
700		308	309
701		314	315

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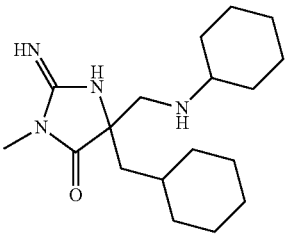
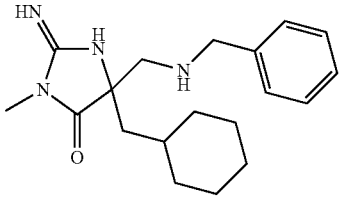
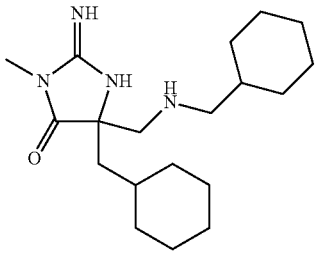
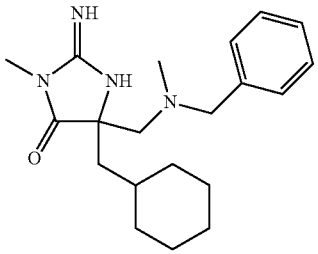
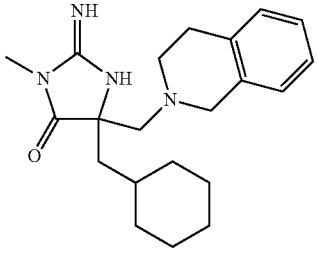
702		320	321
703		328	329
704		334	335
705		342	343
706		354	355

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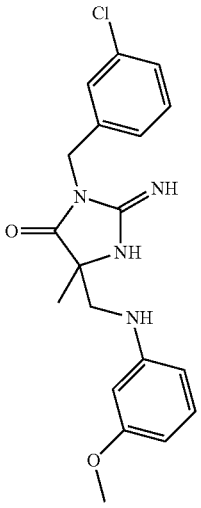
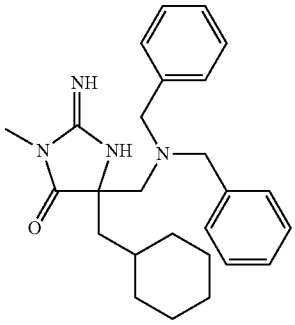
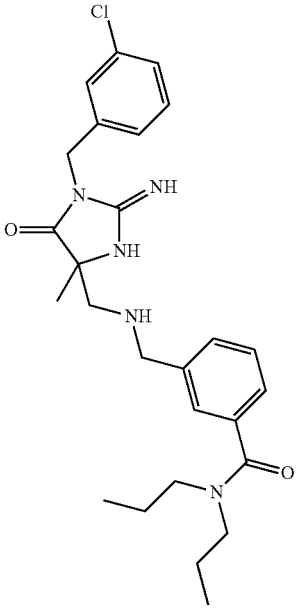
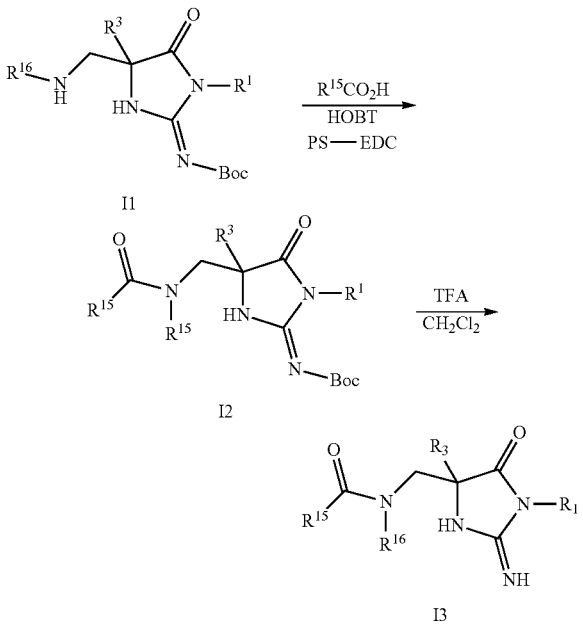
707		372	373
708		418	419
709		483	484

Method I



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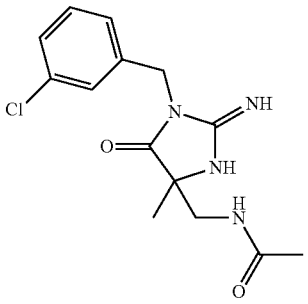
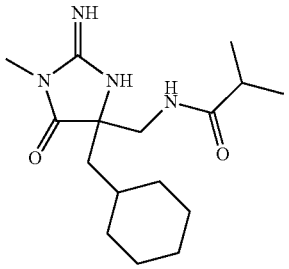
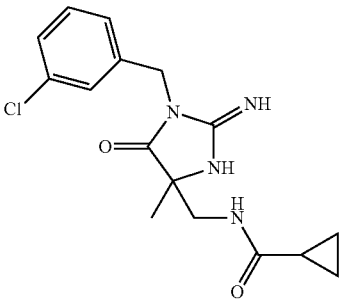
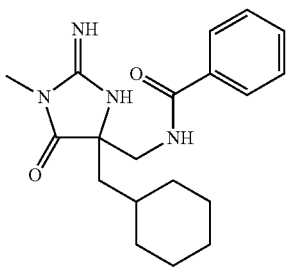
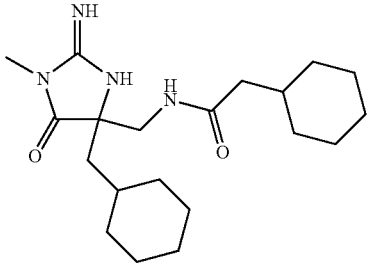
711		308	309
712		308	309
713		334	335
714		342	343
715		362	363

Method I, Step 1:

Diethylaminomethyl polystyrene resin (5 eq) was added to a solution of the formate salt of I1 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3 and R^{16}=H) in CH_2Cl_2 and the suspension was agitated. After 15 min, the mixture was filtered and the resin was washed with CH_2Cl_2 (4×). The filtrate was concentrated to afford the free base I1 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3 and R^{16}=H).

A solution of R^{15}COOH (R^{15}=Phenethyl) (1.3 eq) was added to a mixture of EDC resin (41 mg, 1.53 mmol/g, 3 eq), HOBT (1.5 eq), and the free base of I1 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3 and R^{16}=H) (0.021 mmol) in 1:1 CH_3CN:THF. The suspension was agitated overnight. Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene trisamine resin (40 mg, 6 eq) and a 1:1 mixture of CH_3CN:THF (0.5 mL) was added. The mixture was agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford I2 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, R^{16}=H and R^{15}=$CH_2CH_2C_6H_5$).

Method I, Step 2:

I3 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, R^{16}=H and R^{15}=$CH_2CH_2C_6H_5$) was prepared from I2 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, R^{16}=H and R^{15}=$CH_2CH_2C_6H_5$) using method similar to method H step 6.

The following compounds were prepared using similar method.

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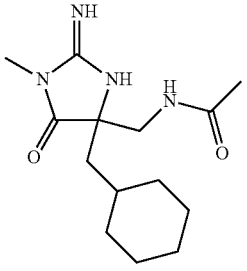
710		280	281

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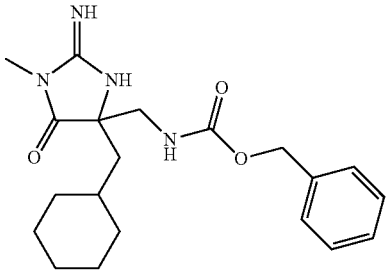
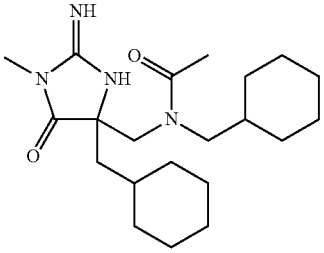
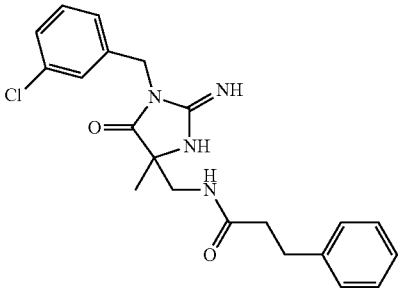
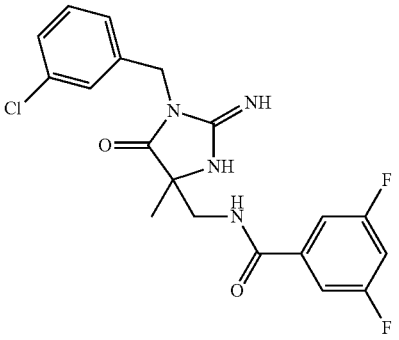
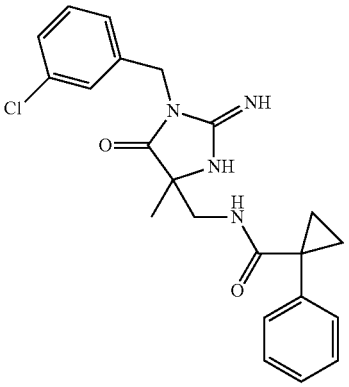
716		372	373
717		376	377
718		398	399
719		406	407
720		410	11

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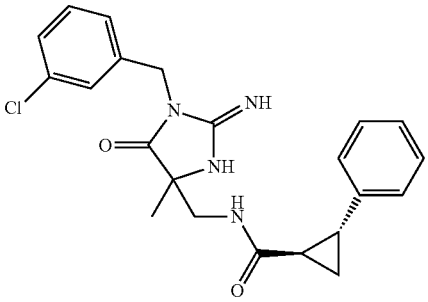
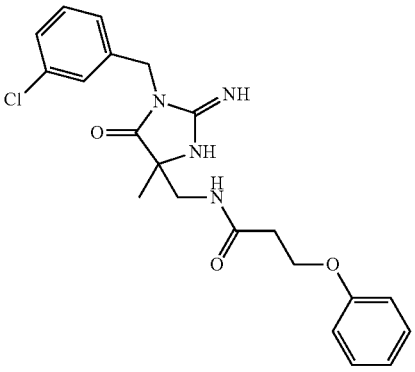
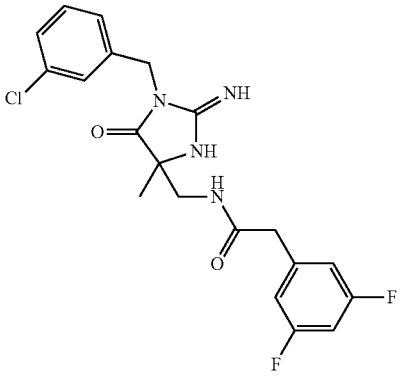
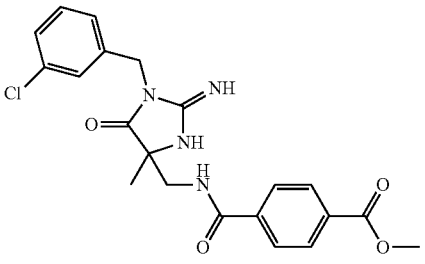
721		410	11
722		414	15
723		420	21
724		428	29

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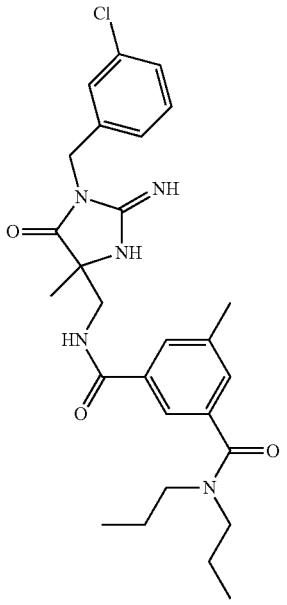
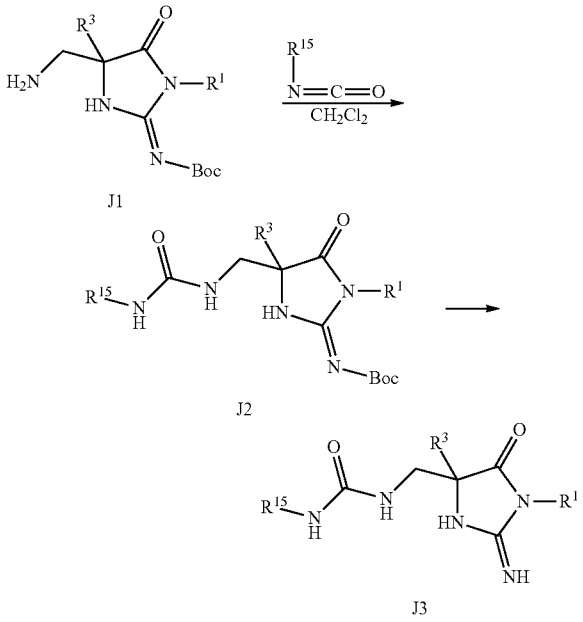
#	Structure	MW	Obs. m/e
725		511	12

Method J



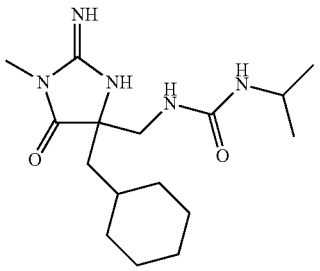
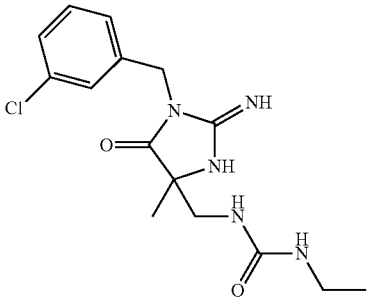
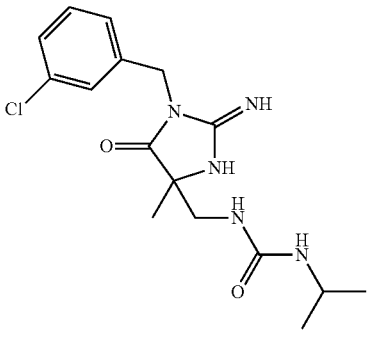
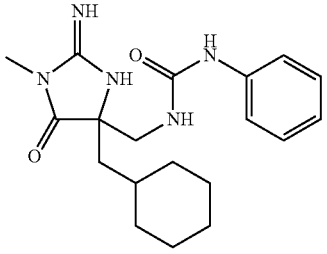
Method J, Step 1:

Diethylaminomethyl polystyrene resin (5 eq) was added to a solution of J1 (TFA salt, R^1=CH_2(3-ClC_6H_4) and R^3=CH_3) in CH_2Cl_2 and the suspension was agitated. After 15 min, the mixture was filtered and the resin was washed with CH_2Cl_2 (4×). The filtrate was concentrated to afford the free base. A solution of R^{15}NCO (R^{15}=butyl) (2 eq) in CH_2Cl_2 was added to the free base of J1 (R^1CH_2(3-ClC_6H_4) and R^3=CH_3) (0.021 mmol) in 1:1 CH_3CN:THF. The suspension was agitated overnight. Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene trisamine resin (40 mg, 6 eq) and a 1:1 mixture of CH_3CN:THF (0.5 mL) was added. The mixture was agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford J2 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, and R^{15}=$CH_2CH_2CH_2CH_3$).

Method J, Step 2:

Compound J3 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, and R^{15}=$CH_2CH_2CH_2CH_3$) was prepared from J2 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, and R^{15}=$CH_2CH_2CH_2CH_3$) following the procedure described in Method H, Step 2.

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e
726		323	324
727		337	338
728		352	
729		358	

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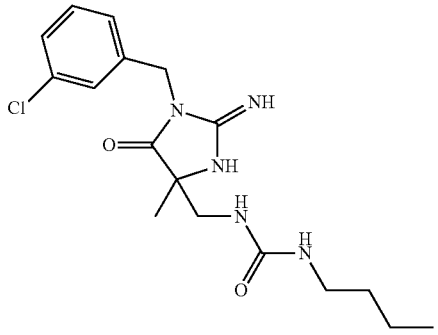
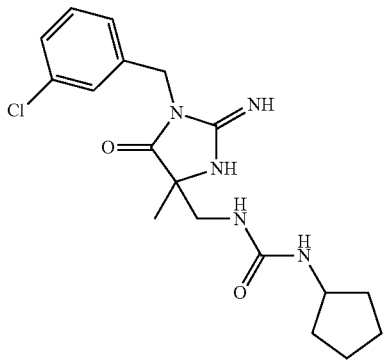
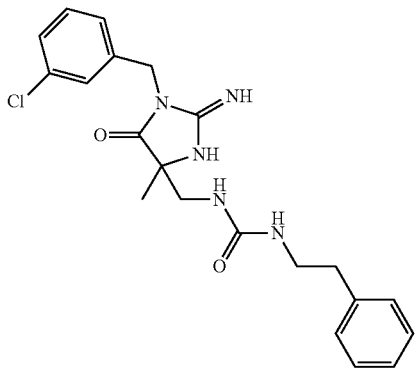
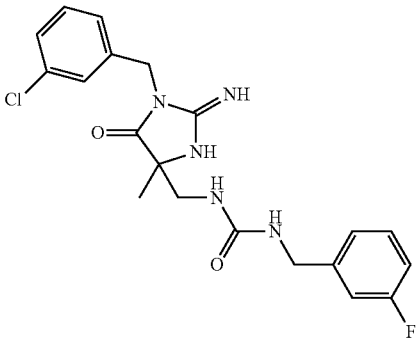
#	Structure	MW	Obs. m/e
730		365	366
731		377	378
732		413	414
733		417	418

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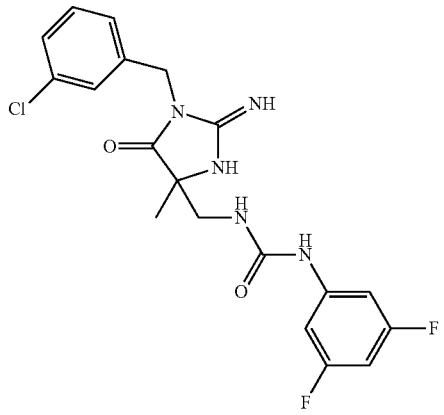
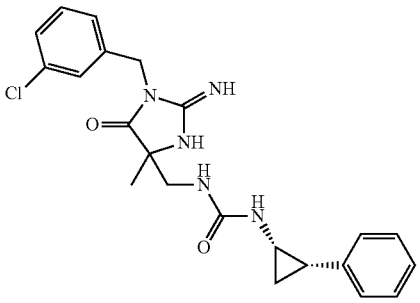
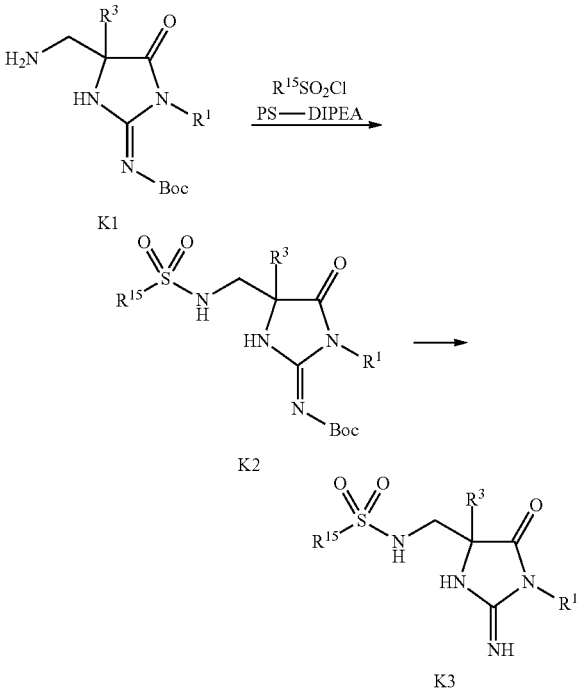
#	Structure	MW	Obs. m/e
734		421	422
735		425	426

Method K



Method K, Step 1:

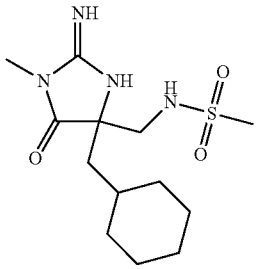
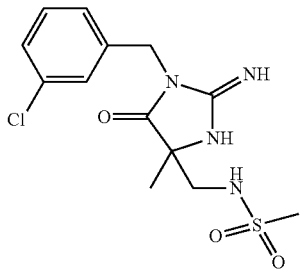
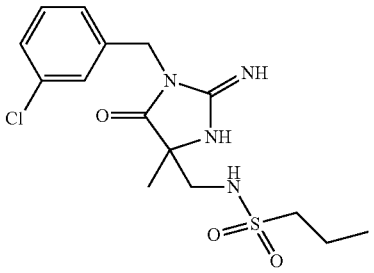
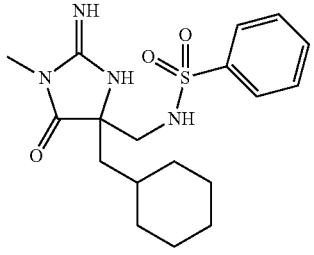
A solution of propyl $R^{15}SO_2Cl$ (R^{15}=Propyl) (1.5 eq) was added to a suspension of polystyrene diisopropylethylamine

resin (18 mg, 3.45 mmol/g, 3 eq) and the free base of K1 prepared using method H (R^1=CH_2(3-ClC_6H_4) and R^3=CH_3) (0.021 mmol) in 1:1 CH_3CN:THF. The suspension was agitated overnight. Polystyrene isocyanate resin (45 mg, 3 eq), polystyrene trisamine resin (40 mg, 6 eq) and a 1:1 mixture of CH_3CN:THF (0.5 mL) was added. The mixture was agitated for 6 h. The suspension was filtered and the filtrate was concentrated to afford K2 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, and R^{15}=$CH_2CH_2CH_3$).

Method K, Step 2:

Compound K3 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, and R^{15}=$CH_2CH_2CH_3$) was prepared from K2 (R^1=CH_2(3-ClC_6H_4), R^3=CH_3, and R^{15}=$CH_2CH_2CH_3$) following the procedure described in Method H, Step 6.

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e
736		316	317
737		344	345
738		372	373
739		378	379

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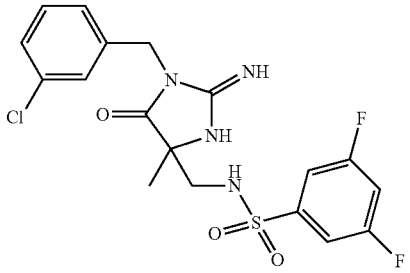
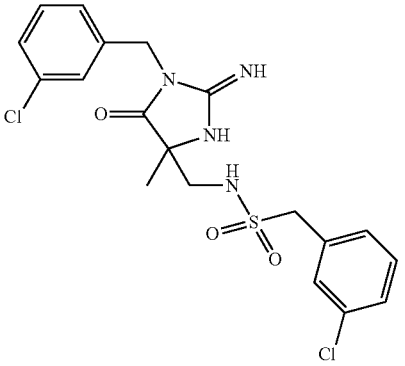
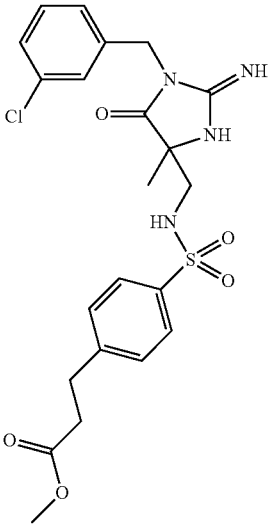
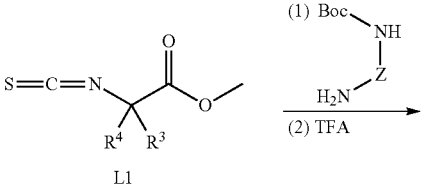
#	Structure	MW	Obs. m/e
740		442	443
741		454	455
742		492	493

Method L



L1

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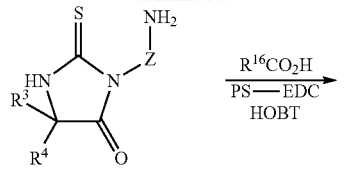
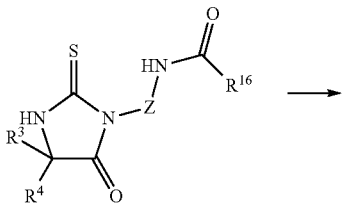
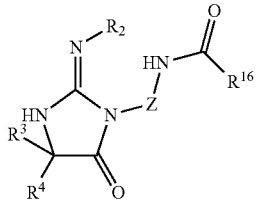


L2



L3



L4

(In the scheme, —Z—NH—C(O)R^{16}— is equivalent to R^1 substituted by R^{21}, or R^1Substituted by alkyl-R^{22}, wherein R^{21} and R^{22} are —N(R^{15})C(O)R^{16} and R^{15} is H, and wherein Z is optionally substituted alkylene-arylenen, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method L, Step 1:

A solution of L1 (R^3=CH_3 and R^4=$CH_2CH(CH_3)_2$) (1 eq) and Z=-para-methylene-benzyl) (1.05 eq) in CH_2Cl_2 was stirred at rt. The reaction solution was concentrated and purified via flash chromatography. The material was treated with 50% trifluoroacetic acid in CH_2Cl_2 for 30 min. The solution was concentrated. The residue was dissolved in 1 N HCl (10 mL) and washed with ether (2×). A saturated solution of Na_2CO_3 in H_2O was added to the aqueous phase until the solution became basic. The solution was extracted with CH_2Cl_2 (3×). The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, filtered and concentrated to yield L2 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—).

Method L, Step 2:

Compound L3 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—, R^{16}=$CH_2CH_2CH_2CH_3$) was prepared from L2 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4$ (CH_2)—) following the procedure described in Method I, Step 1.

Method L, Step 3:

Compound L4 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6NCH_2)$—, R^1=$CH_2CH_2CH_2CH_3$) was prepared from (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4$ (CH_2)—, R^{16}=$CH_2CH_2CH_2CH_3$) following the procedure described in Method A, Step 3.

The following compounds were prepared using similar method.

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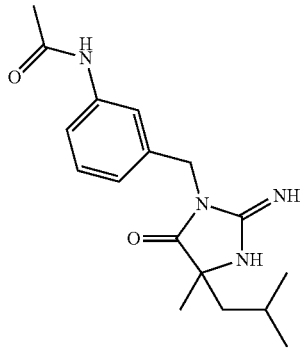
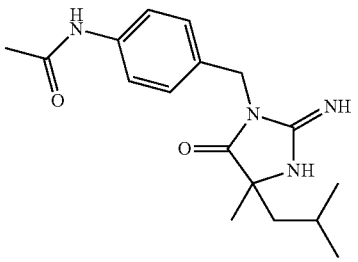
743		316	317
744		316	317

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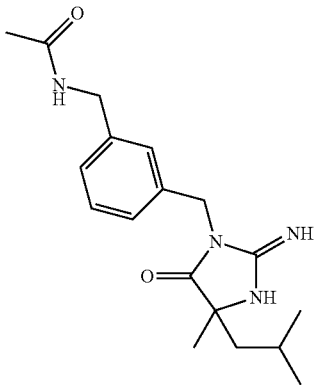
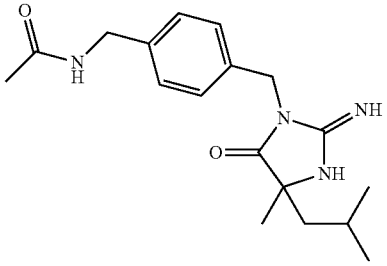
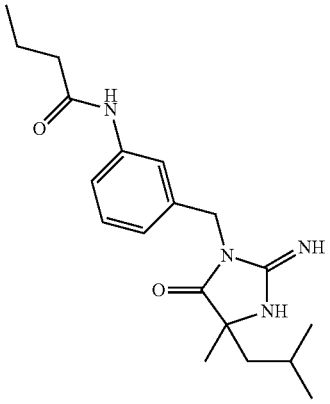
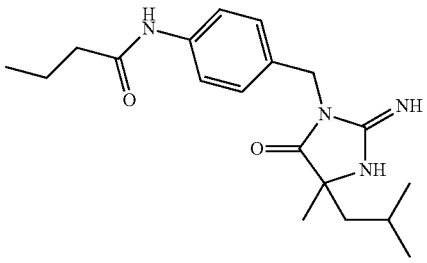
#	Structure	MW	Obs. m/e
745		330	331
746		330	331
747		344	345
748		344	345

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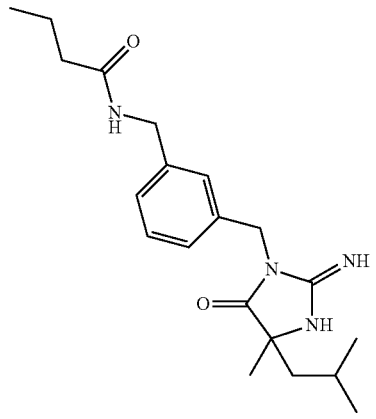
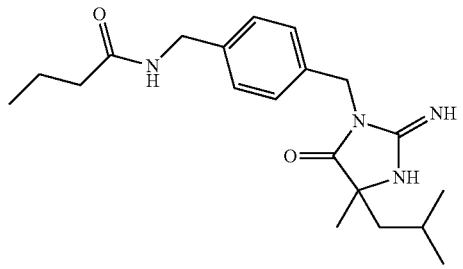
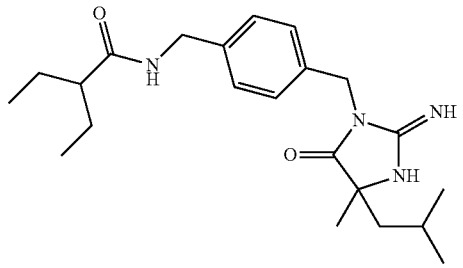
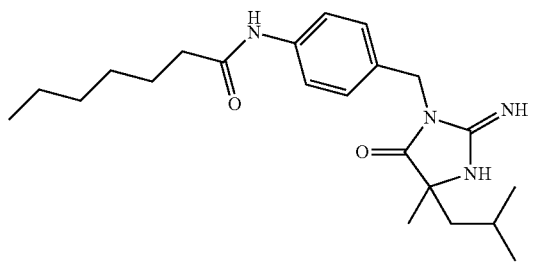
#	Structure	MW	Obs. m/e
749		358	359
750		358	359
751		386	387
752		386	387

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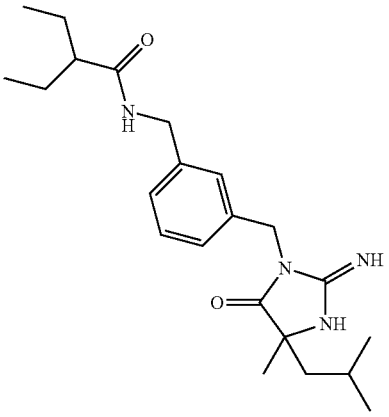
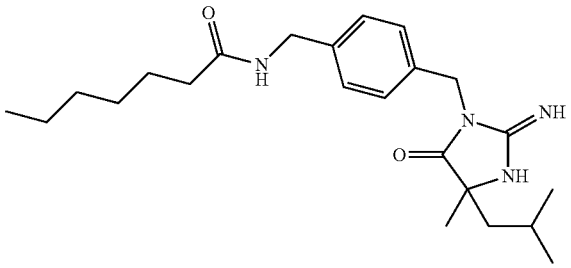
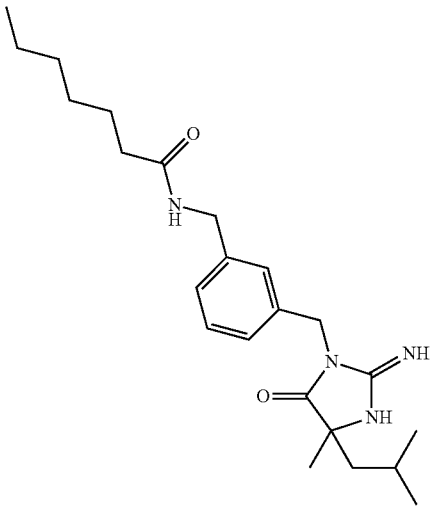
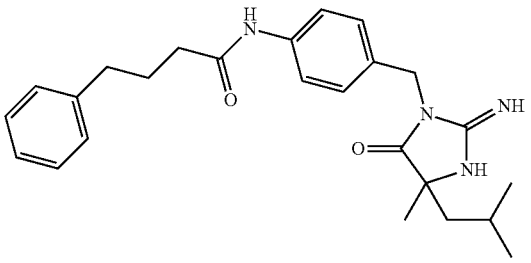
#	Structure	MW	Obs. m/e
753		386	387
754		400	401
755		400	401
756		420	421

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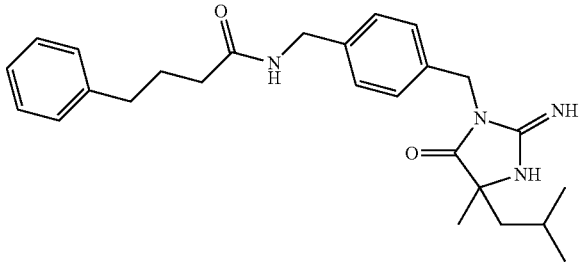
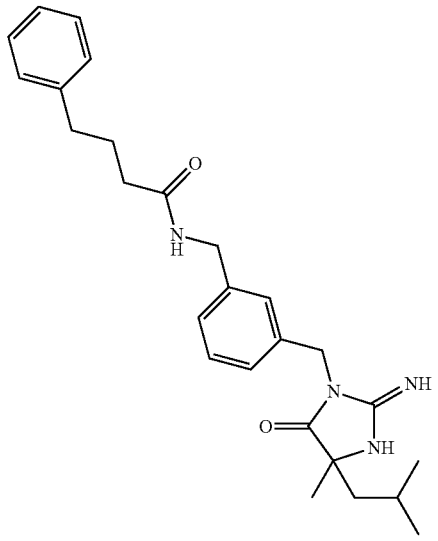
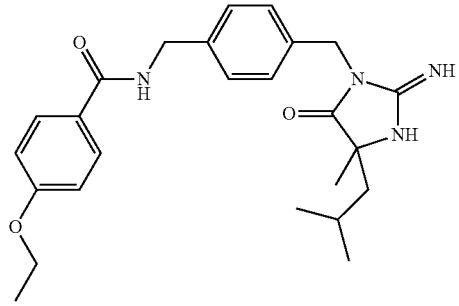
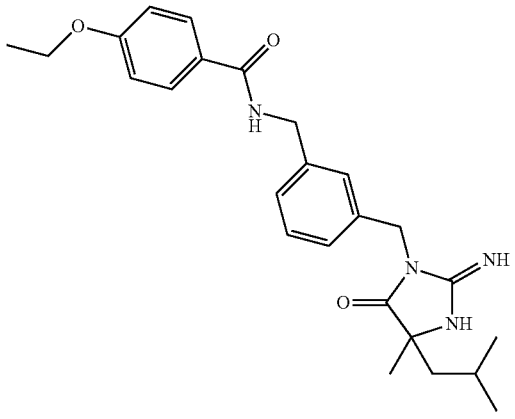
#	Structure	MW	Obs. m/e
757		434	435
758		434	435
759		436	437
760		436	437

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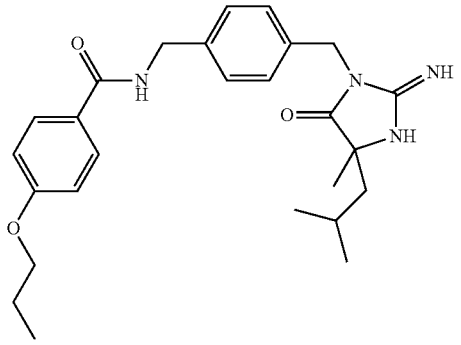
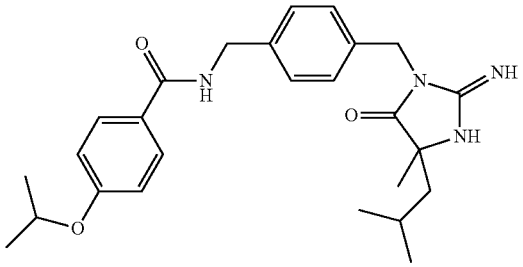
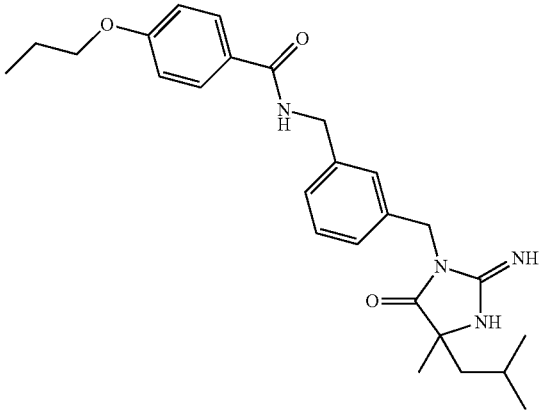
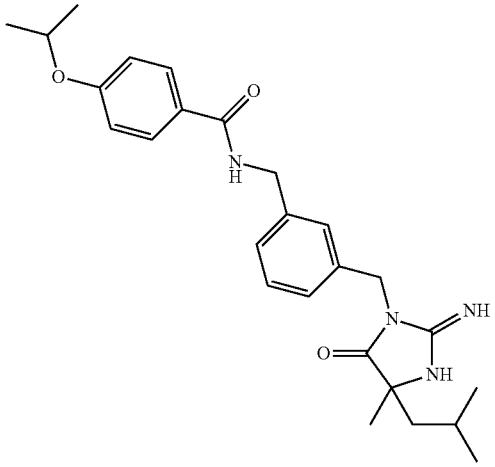
#	Structure	MW	Obs. m/e
761		450	451
762		450	451
763		450	451
764		450	451

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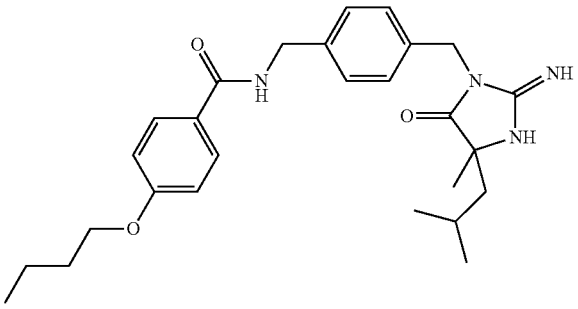
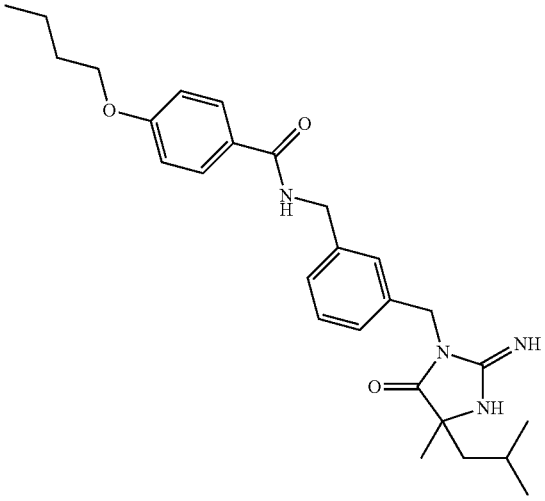
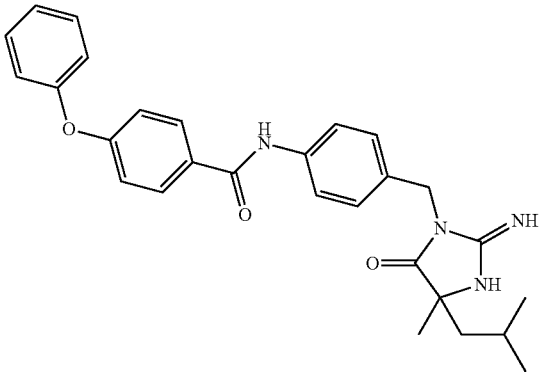
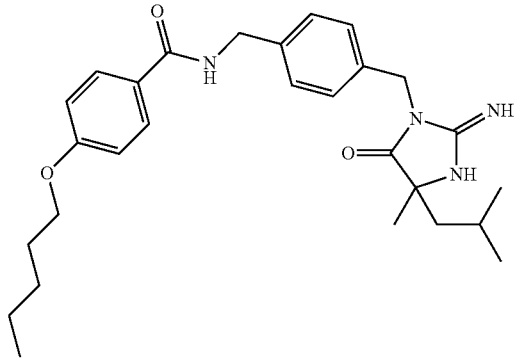
#	Structure	MW	Obs. m/e
765		464	465
766		464	465
767		470	471
768		478	479

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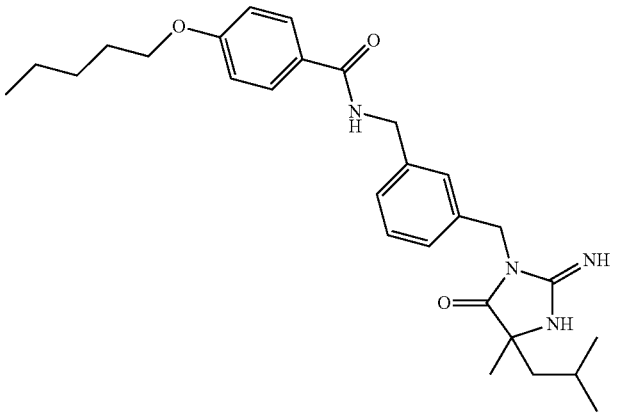
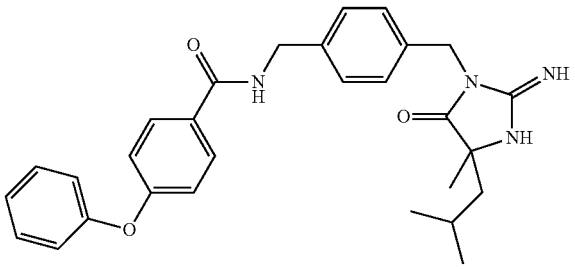
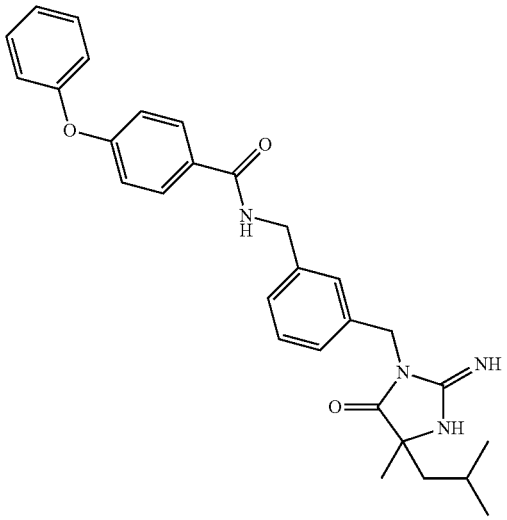
#	Structure	MW	Obs. m/e
769		478	479
770		484	485
771		484	485

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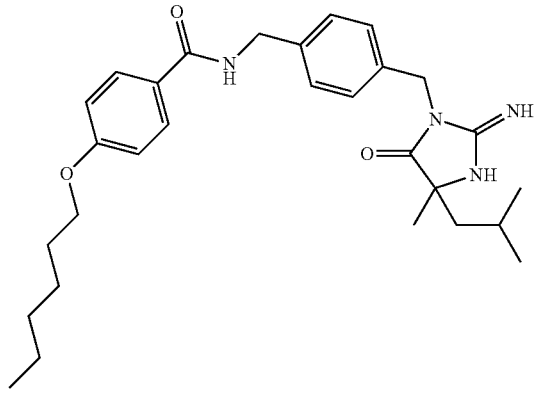
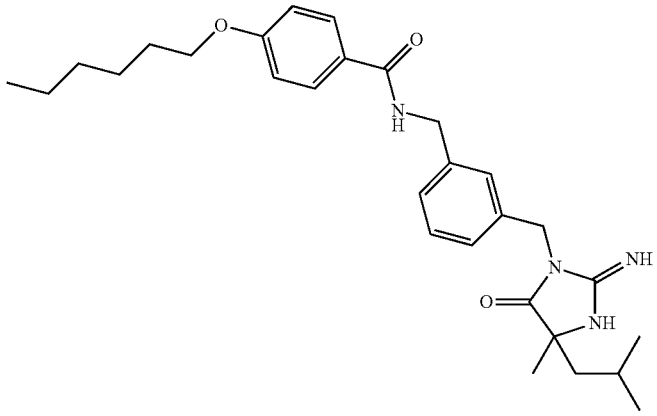
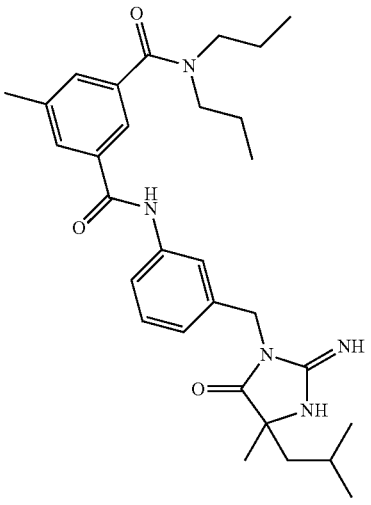
#	Structure	MW	Obs. m/e
772		492	493
773		492	493
774		519	520

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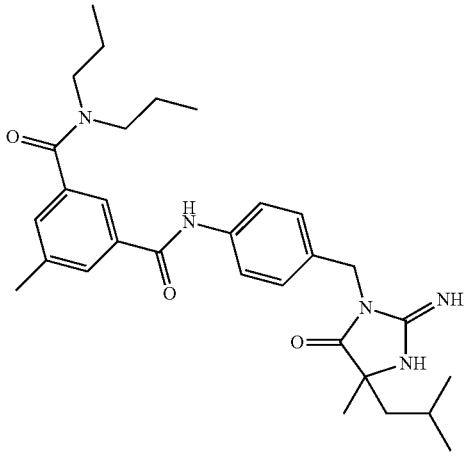
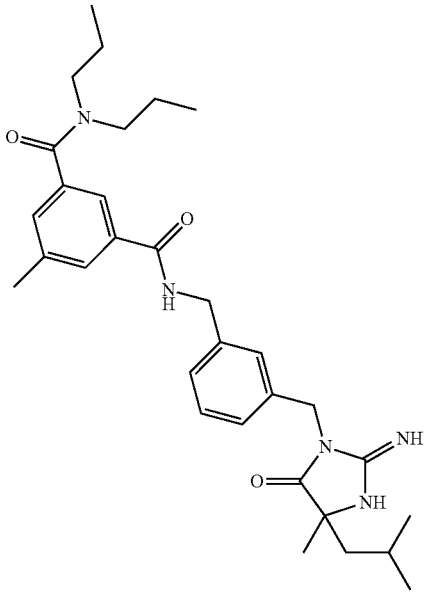
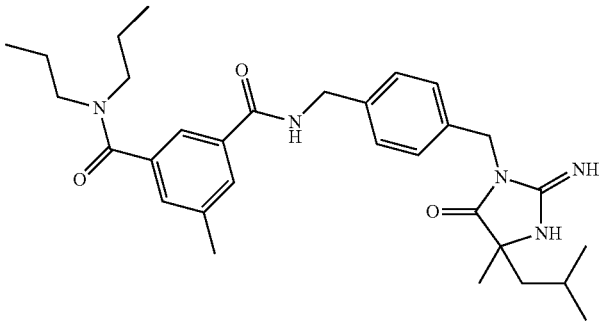
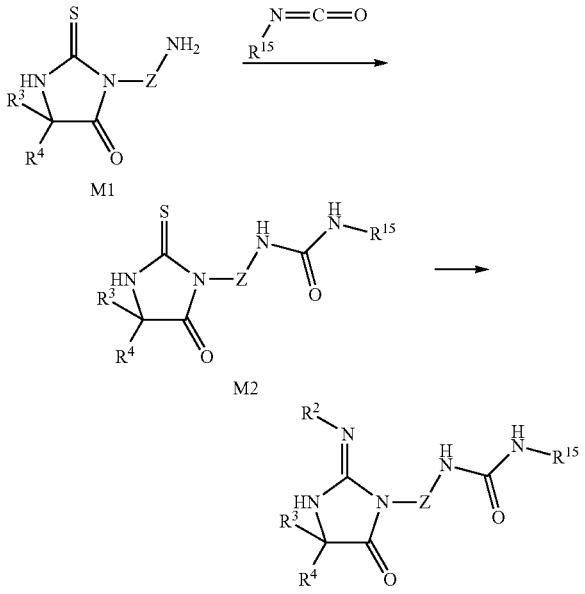
#	Structure	MW	Obs. m/e
775		519	520
776		533	534
777		533	534

Method M



(In the scheme, —Z—NH—C(O)—NHR^{15}— is equivalent to R^1 substituted by R^{21}, or R^1 Substituted by alkyl-R^{22}, wherein R^{21} and R^{22} are —N(R^{16})—C(O)—NHR^{15} and R^{16} is H, and wherein Z is optionally substituted alkylene-arylenene, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

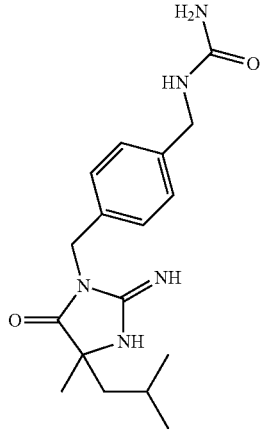
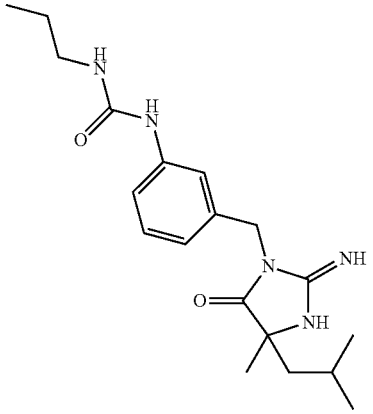
Method M, Step 1:

Compound M2 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—, R^{15}=3,4-difluorophenyl) was prepared from M1 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—) following the procedure described in Method J, Step 1.

Method M, Step 2:

Compound M3 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—, R^{15}=3,4-difluorophenyl) was prepared from M2 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—, R^{15}=3,4-difluorophenyl) following the procedure described in Method A, Step 3. NMR(CD_3OD) δ 7.45, m, 1H; δ 7.26, m, 4H; 7.24, m, 1H; δ 6.96, m, 1H; δ 4.8, m; δ 4.3, s, 2H; δ 1.69, m, 2H; δ 1.44, m, 1H; δ 1.37, s, 3H; δ 0.8, m, 3H; δ 0.63, m, 3H. ES_LCMS (m/e) 430.27

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e
778		331	332
779		359	360

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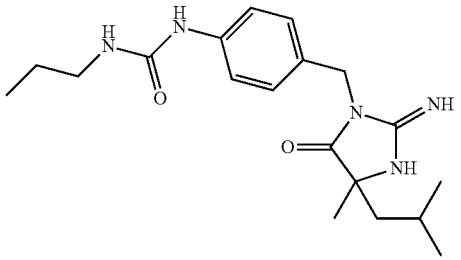
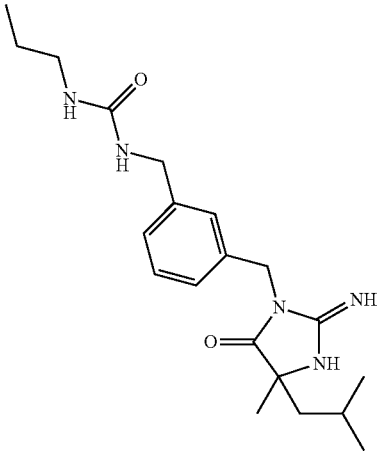
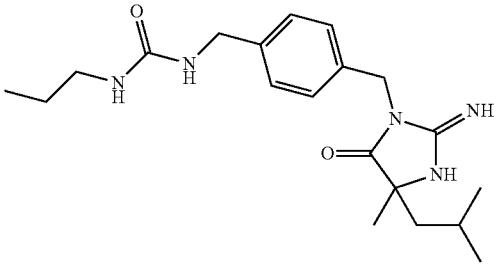
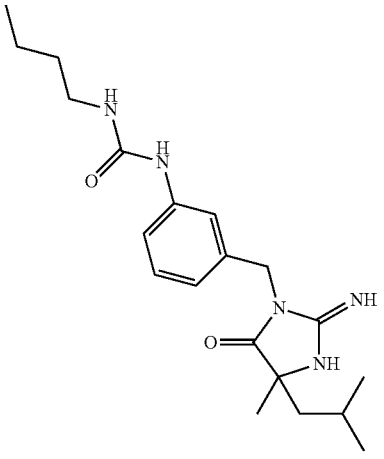
#	Structure	MW	Obs. m/e
780		359	360
781		373	374
782		373	374
783		373	374

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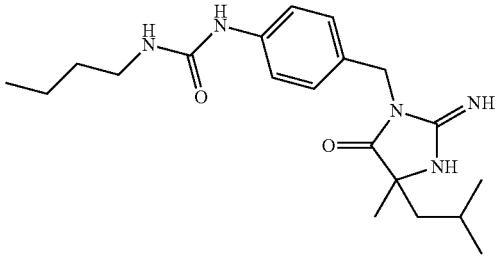
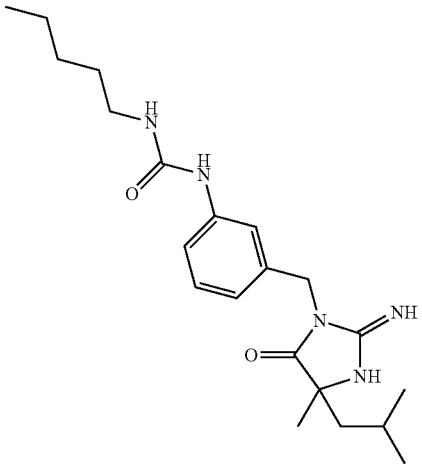
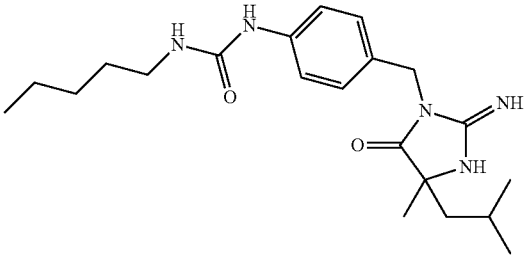
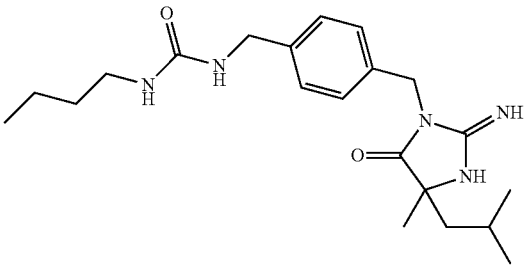
#	Structure	MW	Obs. m/e
784		373	374
785		387	388
786		387	388
787		387	388

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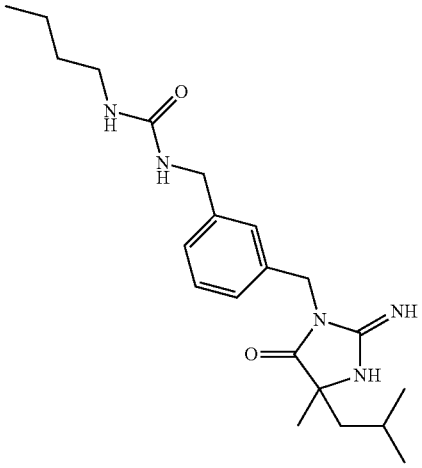
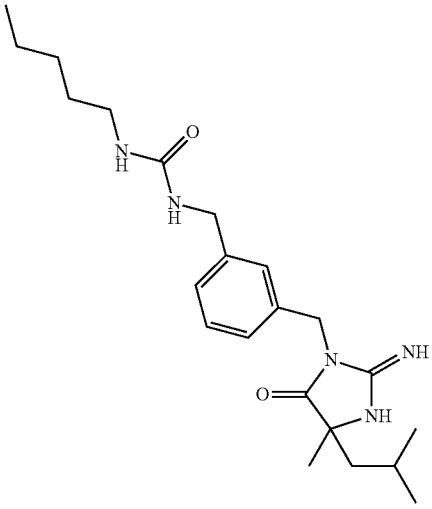
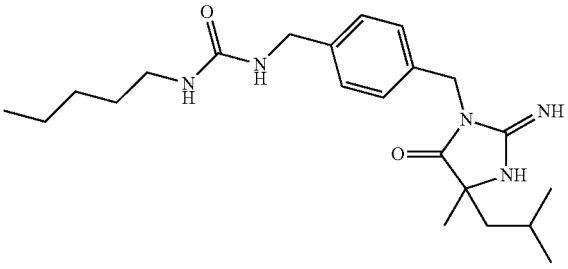
#	Structure	MW	Obs. m/e
788		387	388
789		401	402
790		401	402

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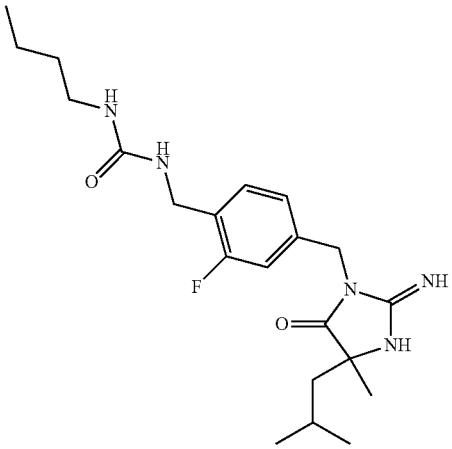
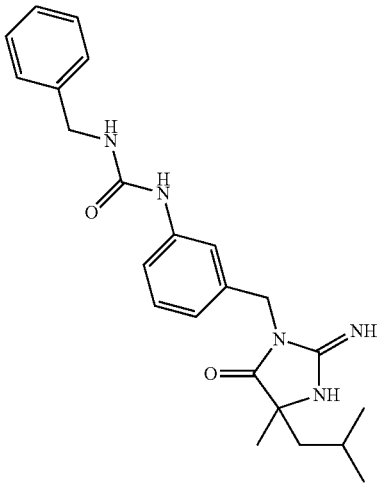
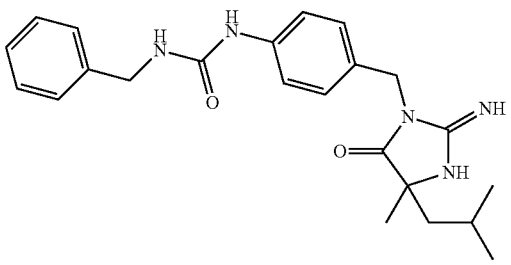
#	Structure	MW	Obs. m/e
791		405	406
792		407	408
793		407	408

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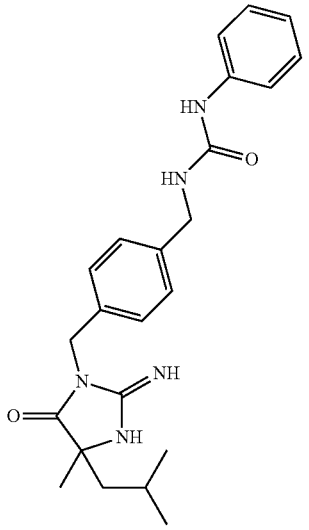
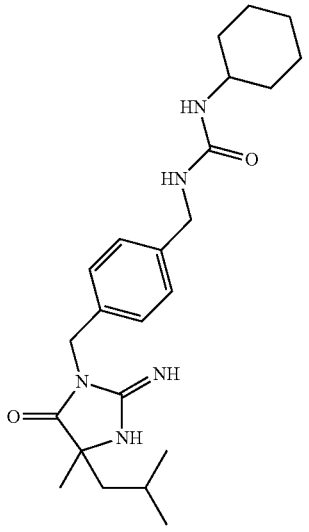
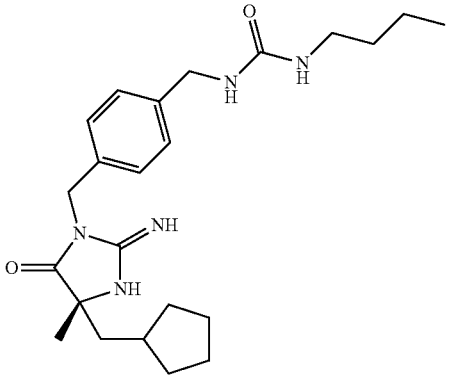
#	Structure	MW	Obs. m/e
794		407	408
795		413	414
796		413	414

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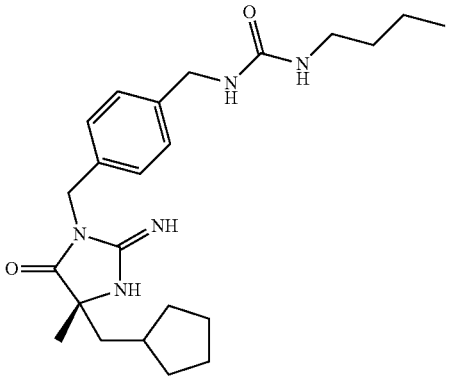
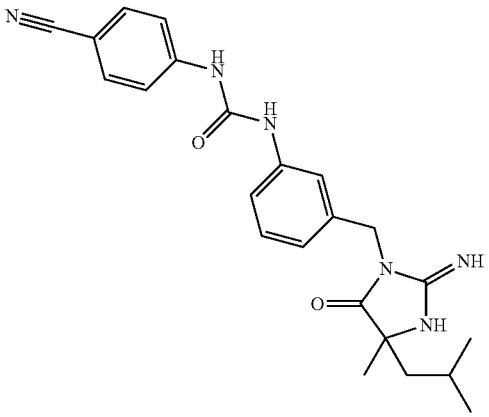
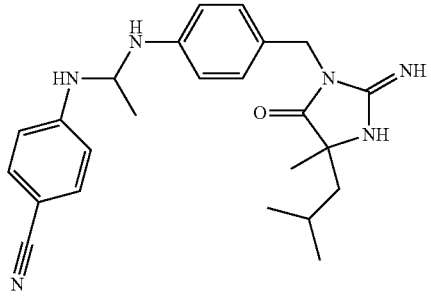
#	Structure	MW	Obs. m/e
796		413	414
797		418	419
798		418	419

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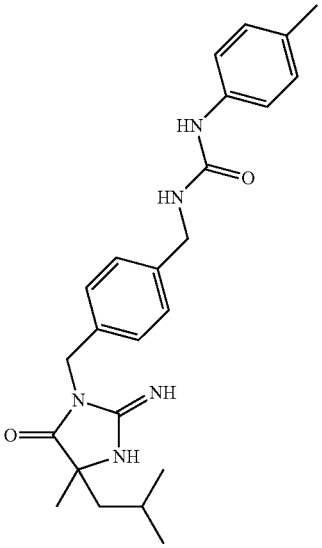
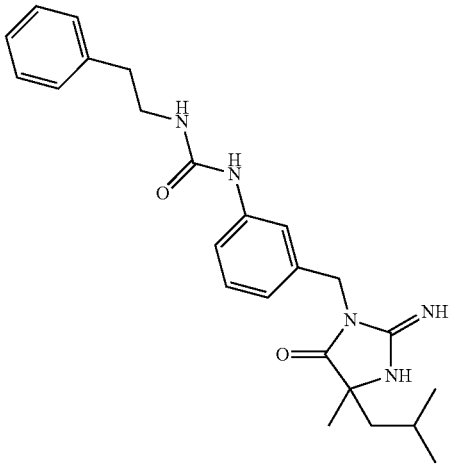
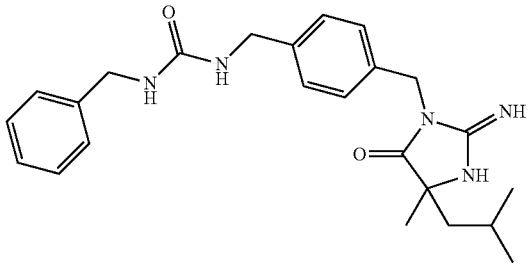
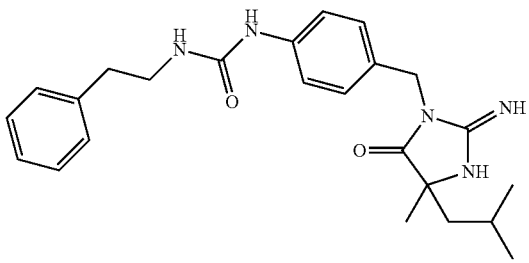
#	Structure	MW	Obs. m/e
799		421	422
800		421	422
801		421	422
802		421	422

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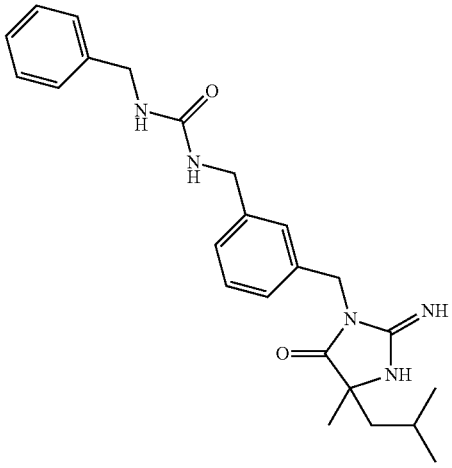
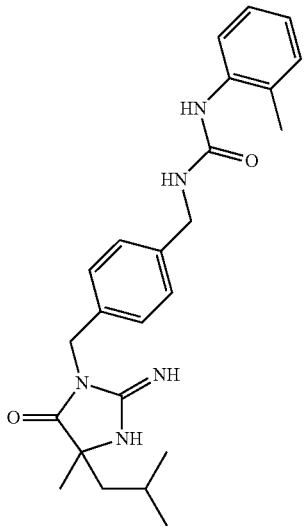
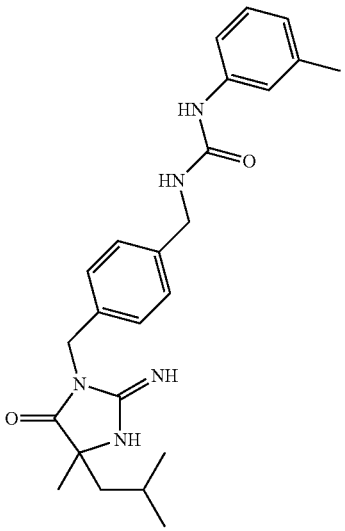
#	Structure	MW	Obs. m/e
803		421	422
804		421	422
805		421	422

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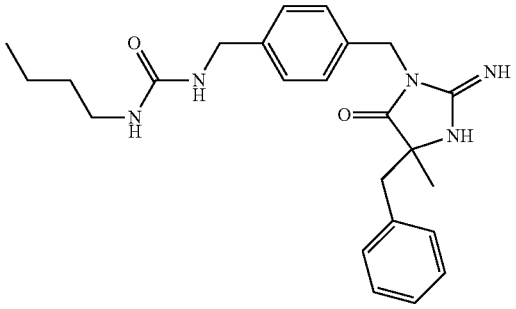
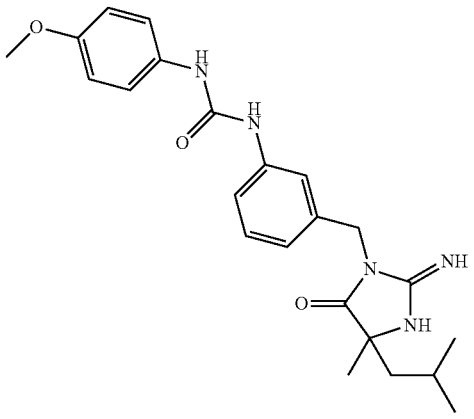
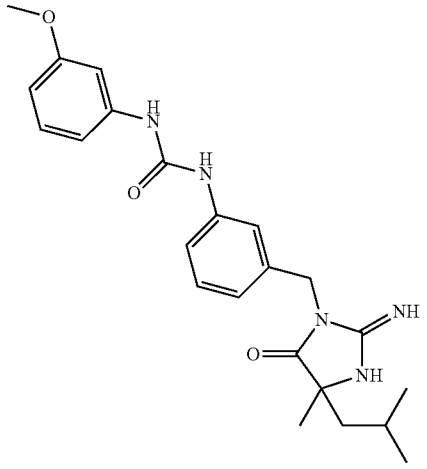
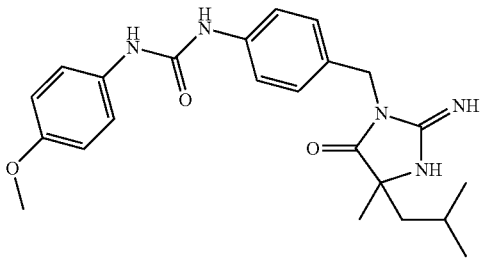
#	Structure	MW	Obs. m/e
806		421	422
807		423	424
808		423	424
809		423	424

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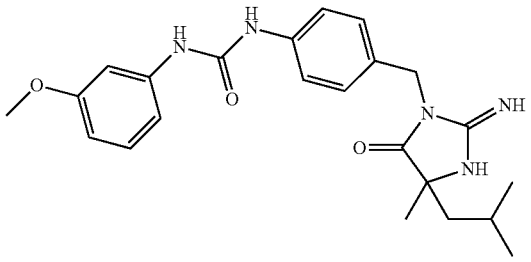
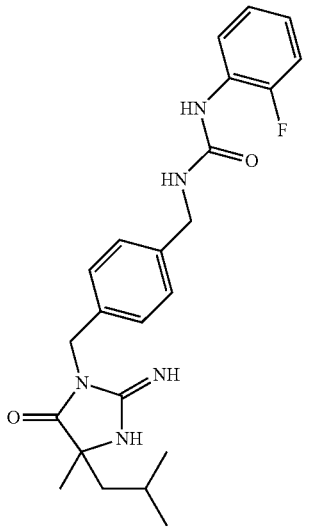
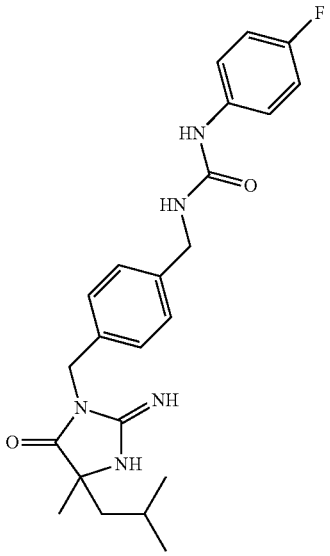
#	Structure	MW	Obs. m/e
810		423	424
811		425	426
812		425	426

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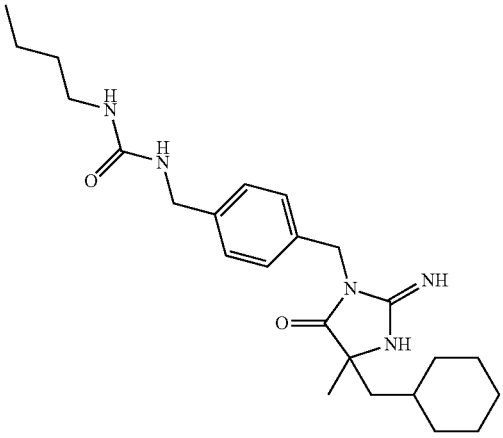
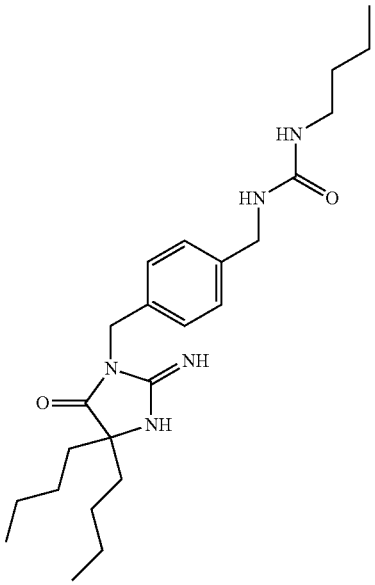
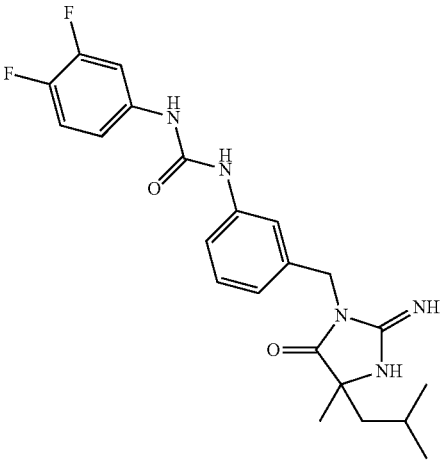
#	Structure	MW	Obs. m/e
813		427	428
814		429	430
815		429	430

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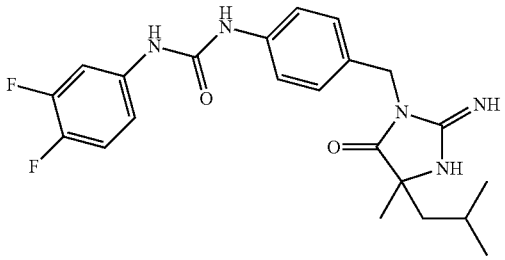
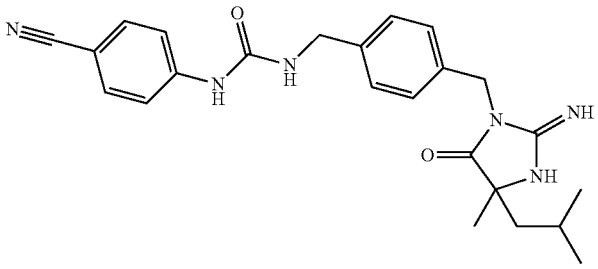
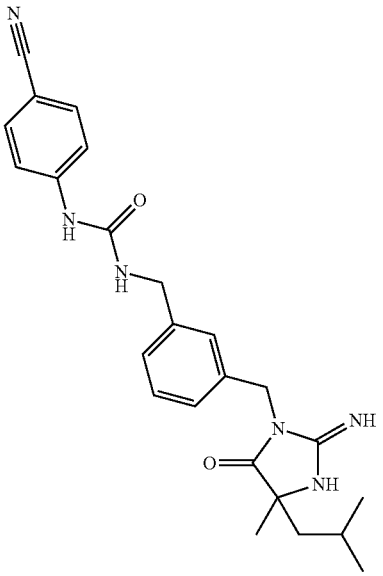
#	Structure	MW	Obs. m/e
816		429	430
817		432	433
818		432	433

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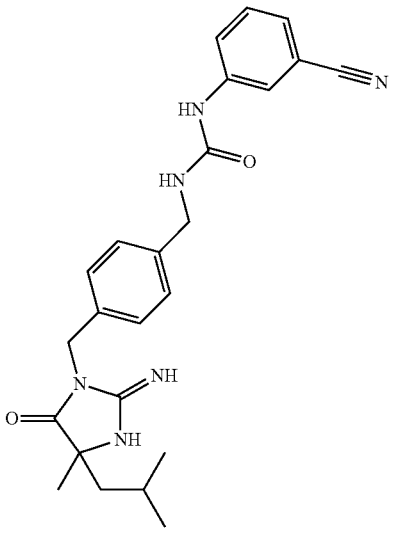
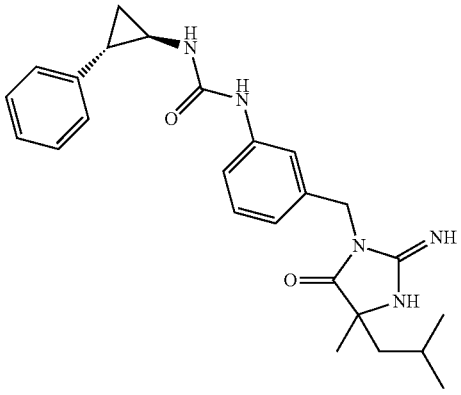
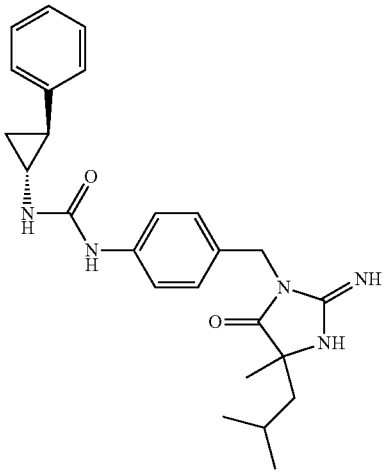
#	Structure	MW	Obs. m/e
819		432	433
820		433	434
821		433	434

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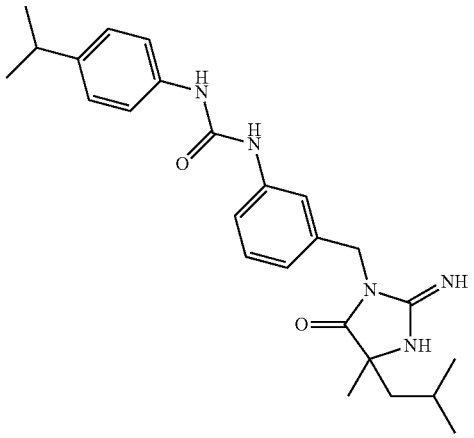
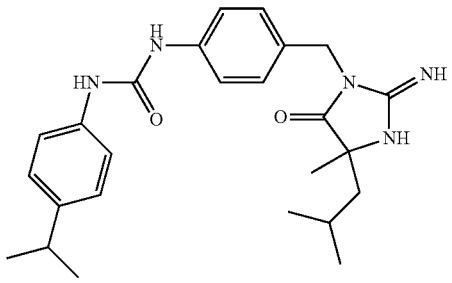
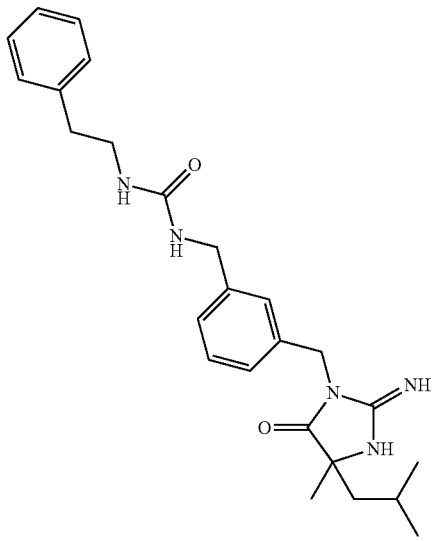
#	Structure	MW	Obs. m/e
822		435	436
823		435	436
824		435	436

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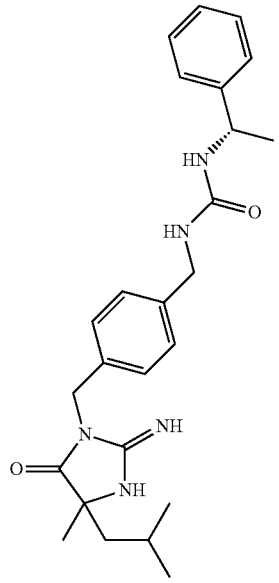
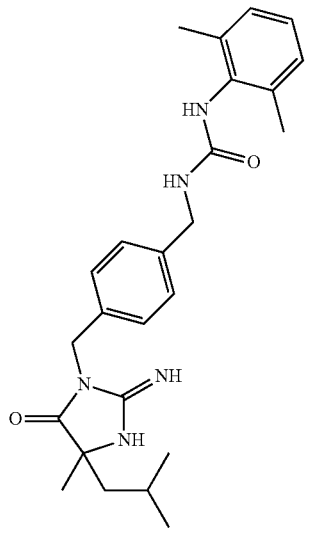
#	Structure	MW	Obs. m/e
825		435	436
826		435	436

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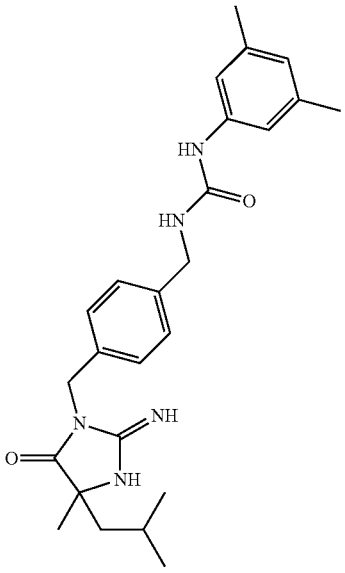
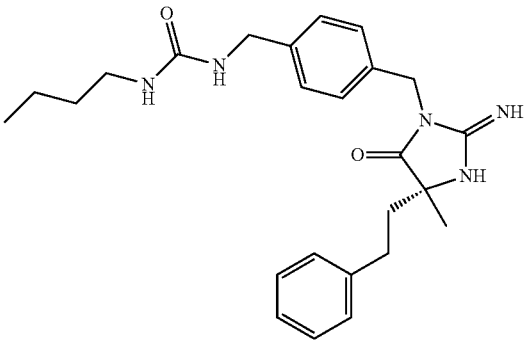
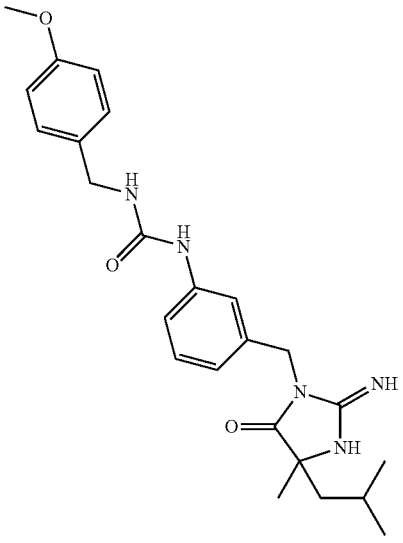
#	Structure	MW	Obs. m/e
827		435	436
828		435	436
829		437	438

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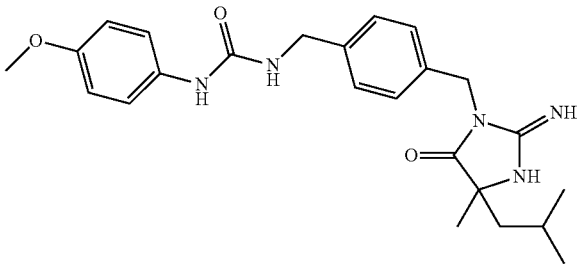
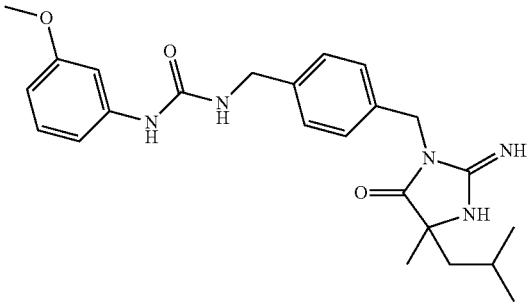
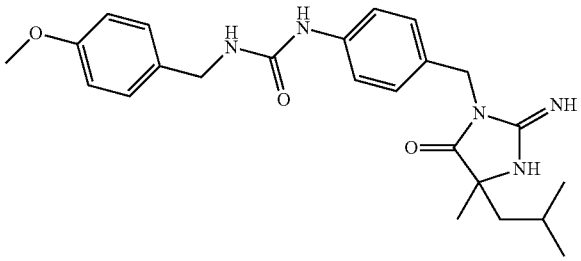
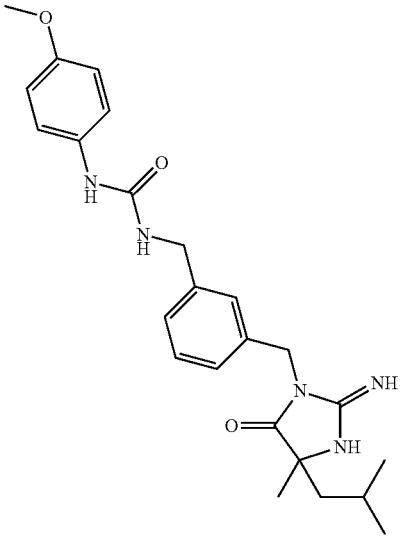
#	Structure	MW	Obs. m/e
830		437	438
831		437	438
832		437	438
833		437	438

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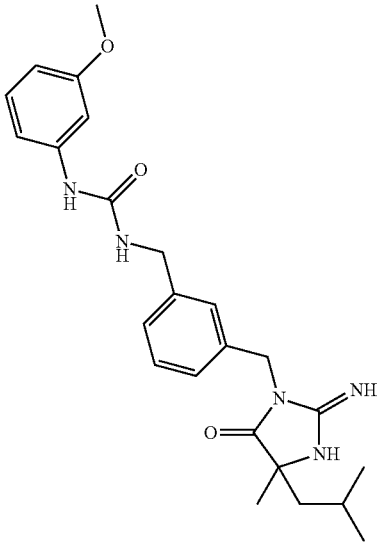
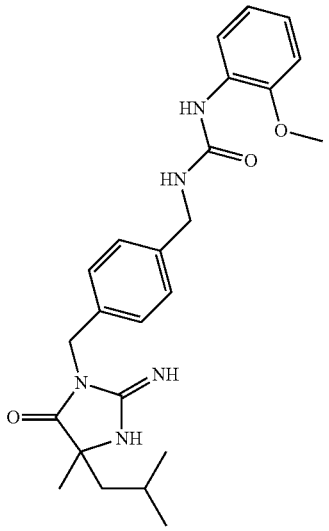
#	Structure	MW	Obs. m/e
834		437	438
835		437	438

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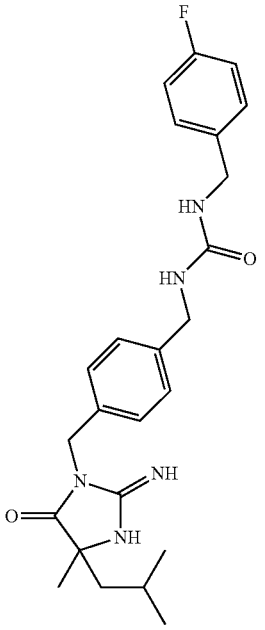
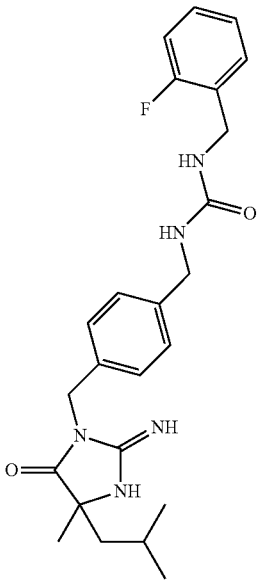
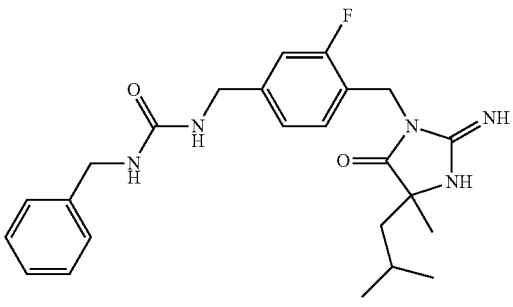
#	Structure	MW	Obs. m/e
836		439	440
837		439	440
838		439	440

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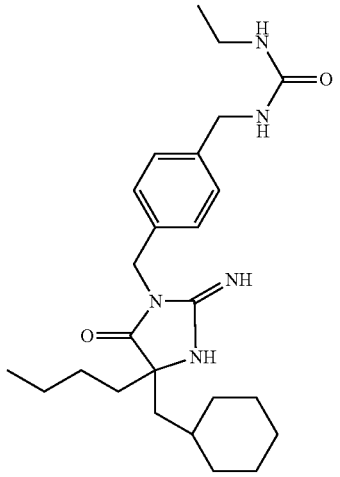
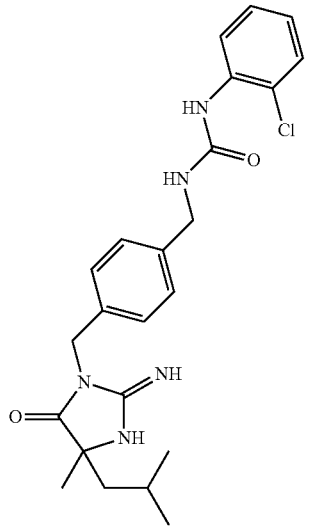
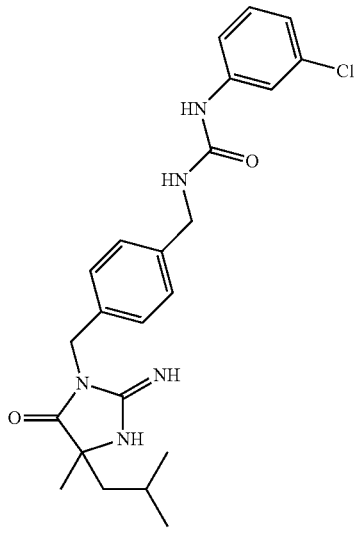
#	Structure	MW	Obs. m/e
839		441	442
840		441	442
841		441	442

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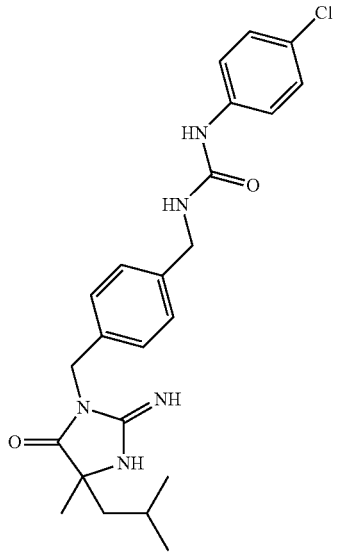
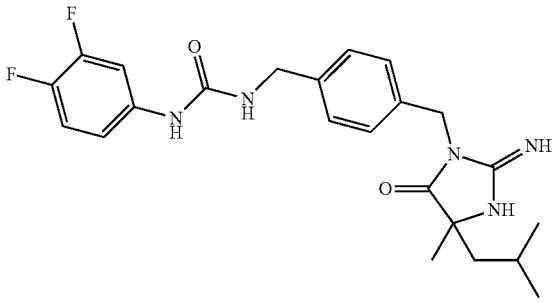
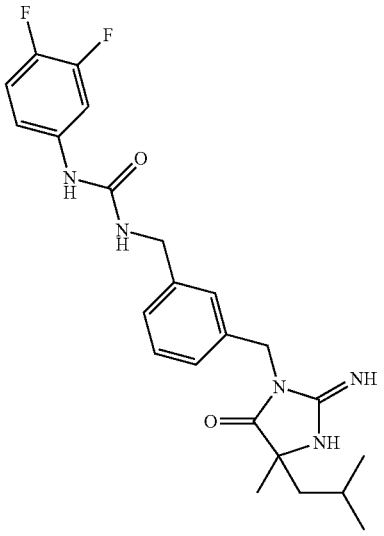
#	Structure	MW	Obs. m/e
842		441	442
843		443	444
844		443	444

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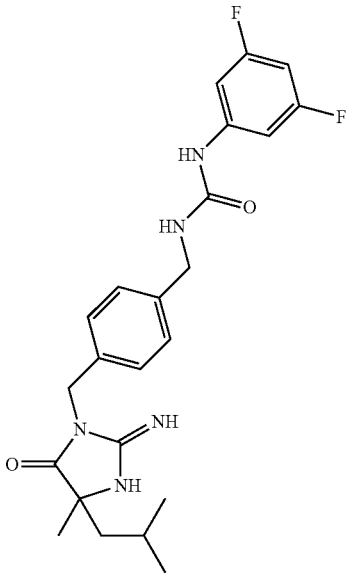
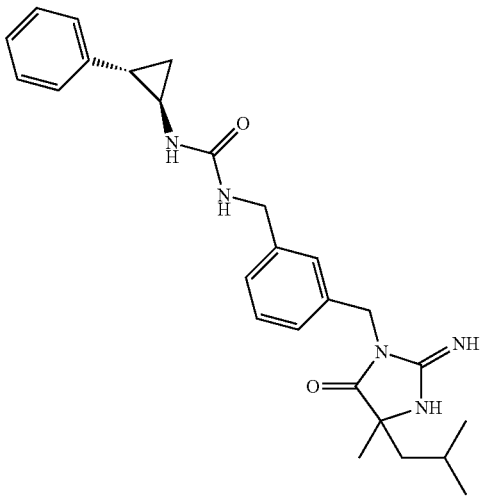
#	Structure	MW	Obs. m/e
845		443	444
846		447	448

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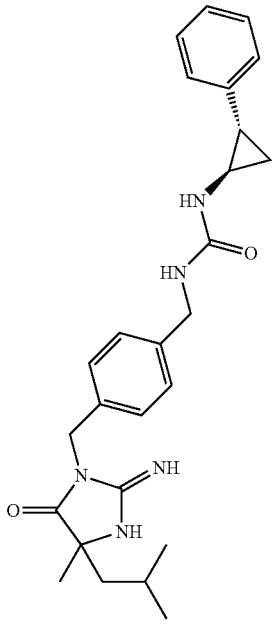
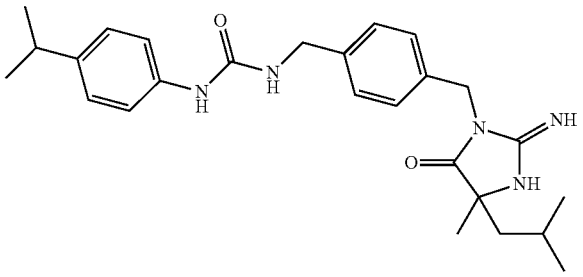
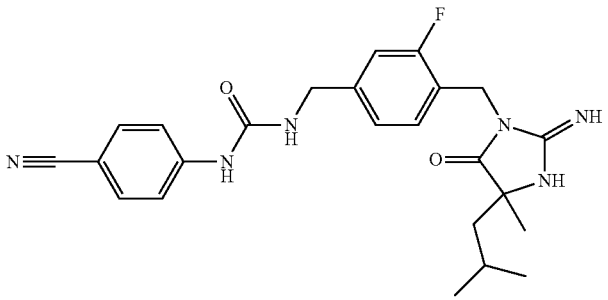
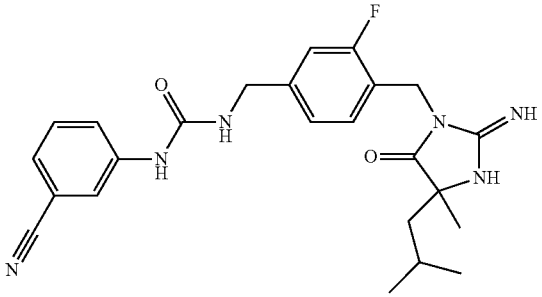
#	Structure	MW	Obs. m/e
847		447	448
848		449	450
849		450	451
850		450	451

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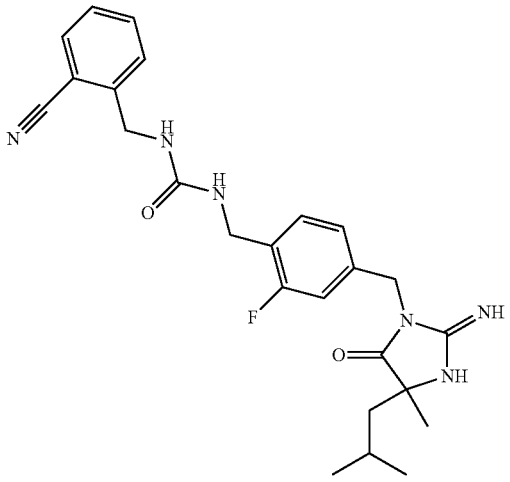
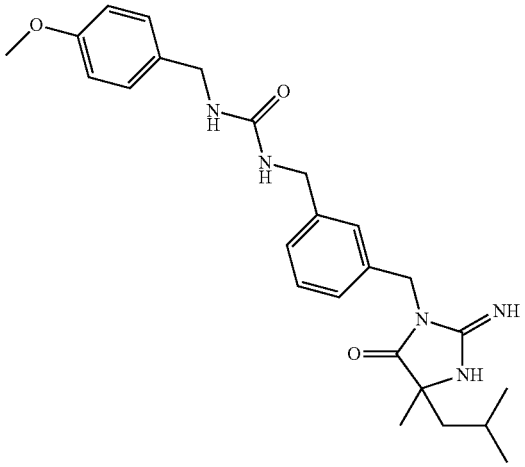
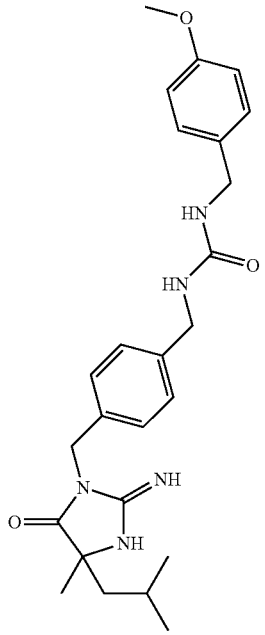
#	Structure	MW	Obs. m/e
851		450	451
852		451	452
853		451	452

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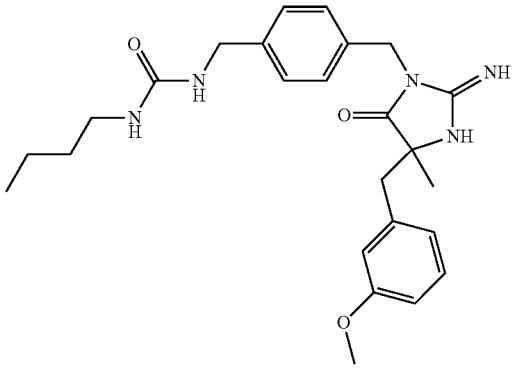
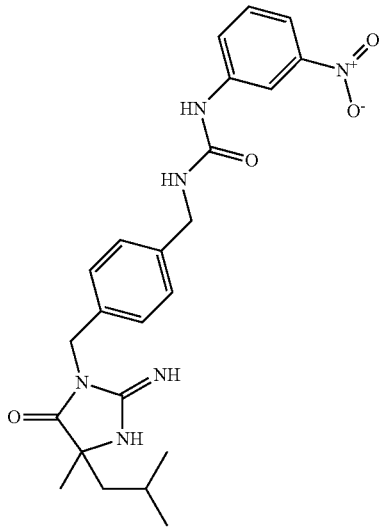
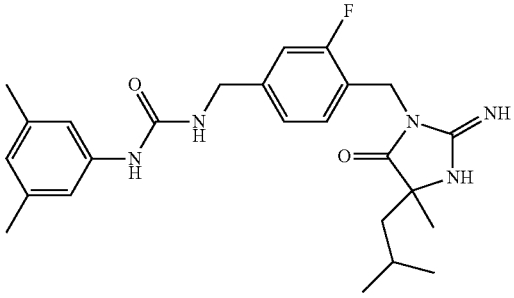
#	Structure	MW	Obs. m/e
854		451	452
855		452	453
856		453	454

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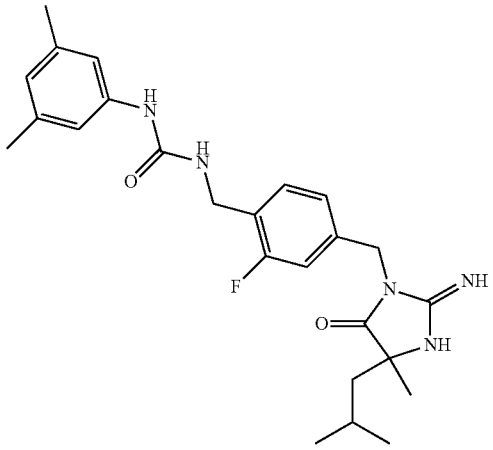
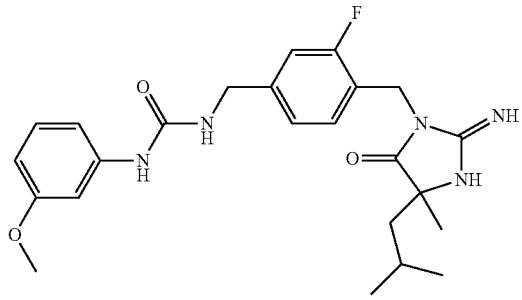
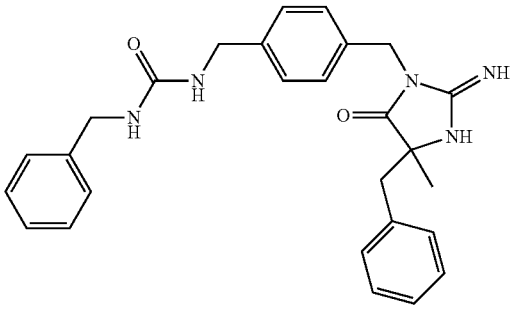
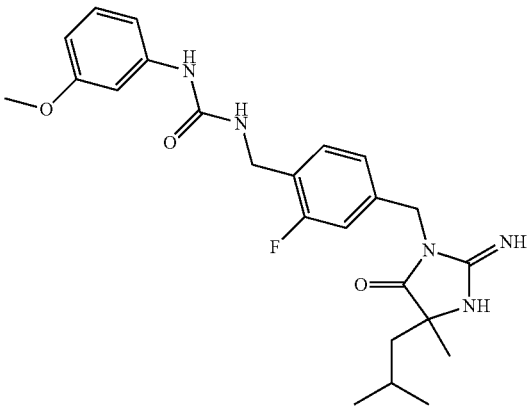
#	Structure	MW	Obs. m/e
857		453	454
858		455	456
859		455	456
860		455	456

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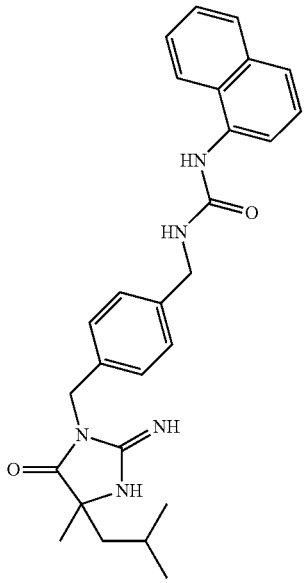
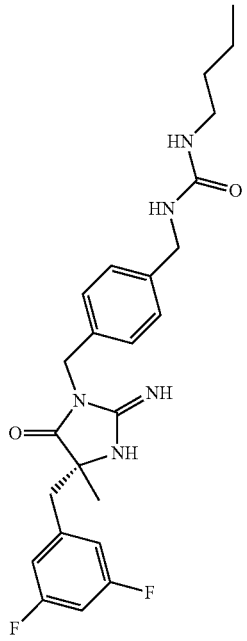
#	Structure	MW	Obs. m/e
861		457	458
862		457	458

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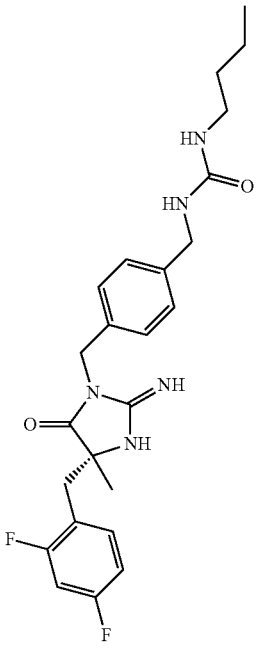
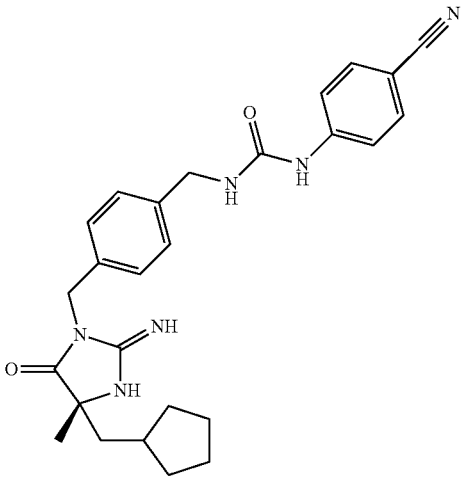
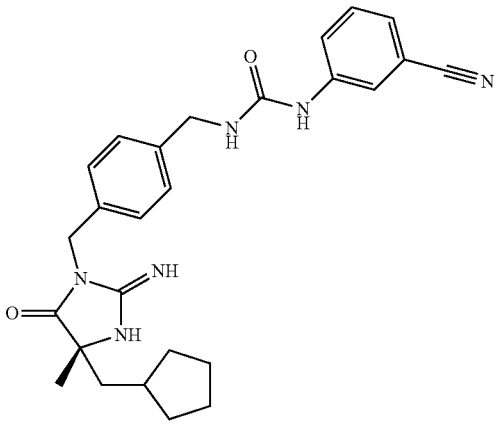
#	Structure	MW	Obs. m/e
863		457	458
864		458	459
865		458	459

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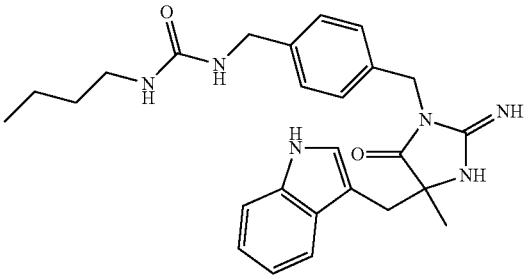
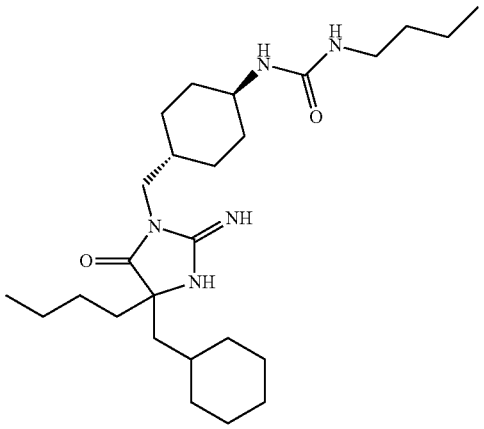
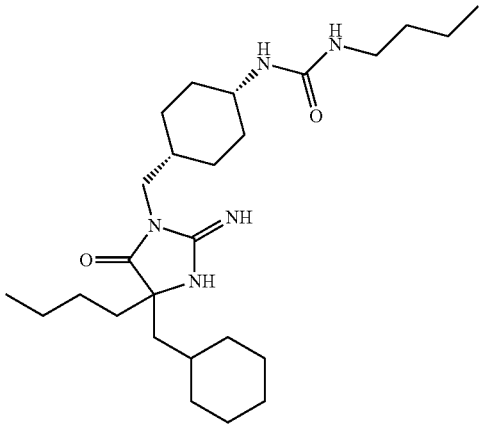
#	Structure	MW	Obs. m/e
866		460	461
867		461	462
868		461	462

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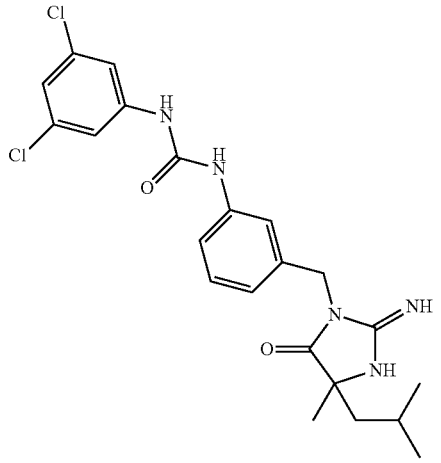
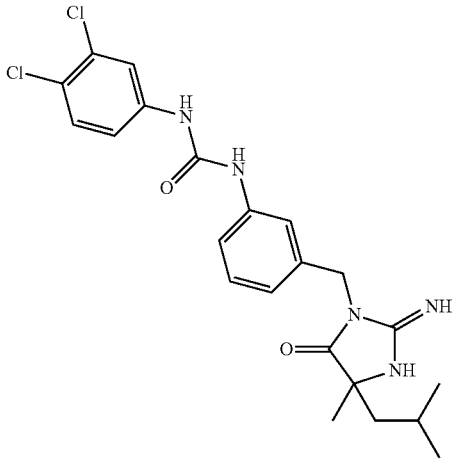
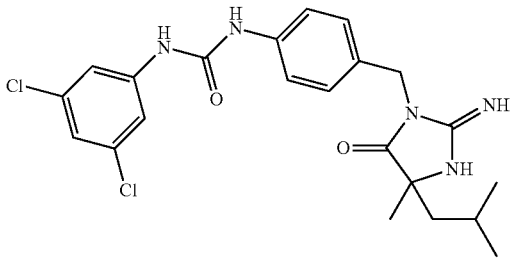
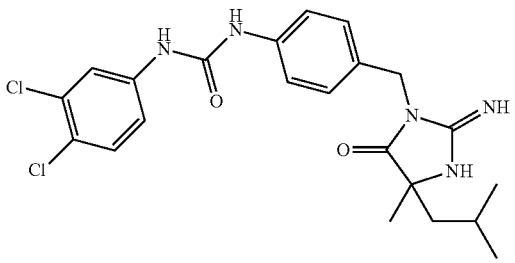
#	Structure	MW	Obs. m/e
869		461	462
870		461	462
871		461	462
872		461	462

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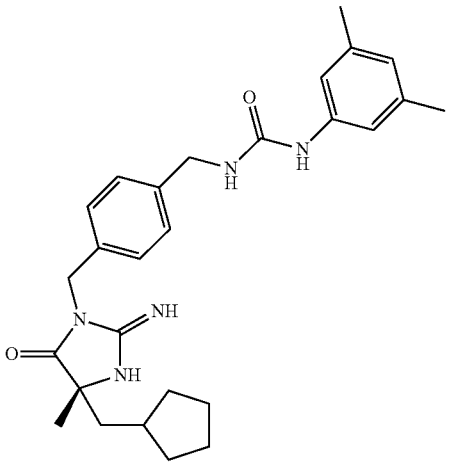
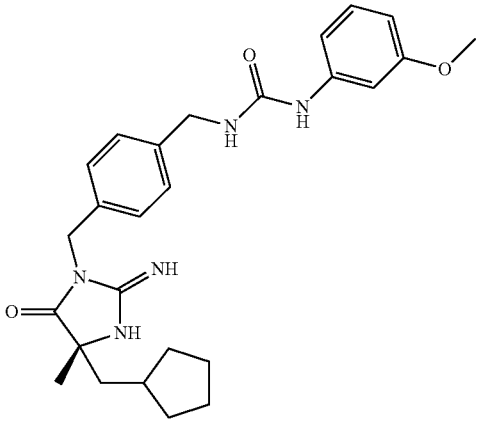
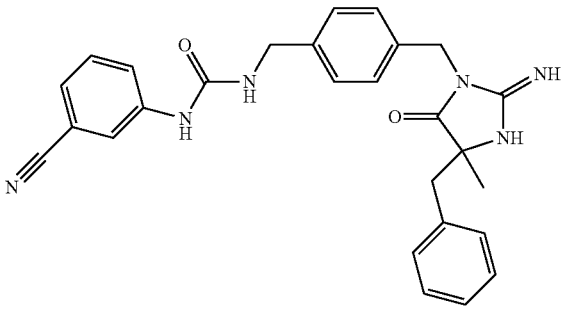
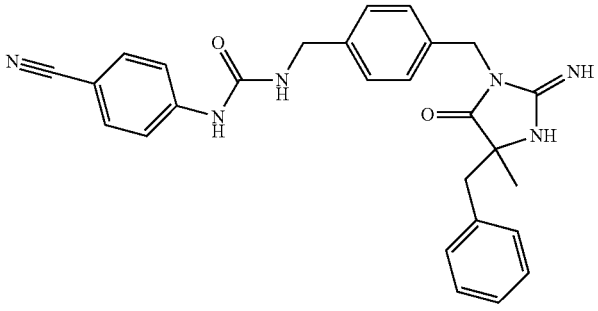
#	Structure	MW	Obs. m/e
873		461	462
874		463	464
875		466	467
876		466	467

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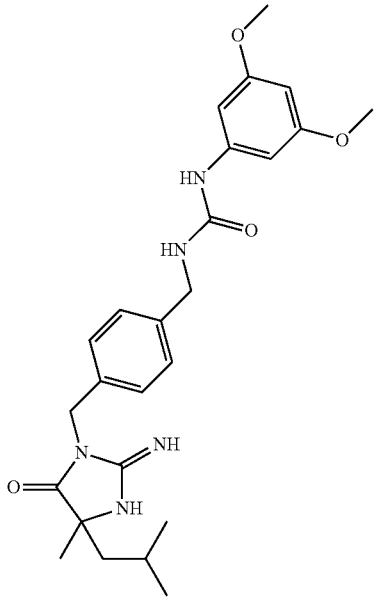
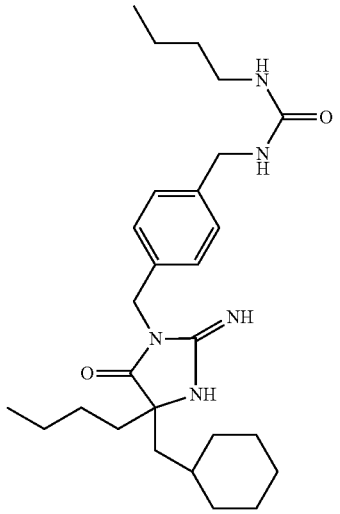
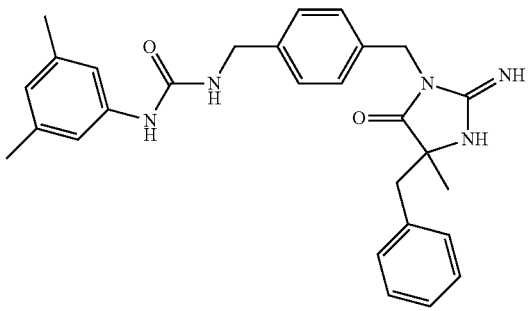
#	Structure	MW	Obs. m/e
877		467	468
878		469	470
879		469	470

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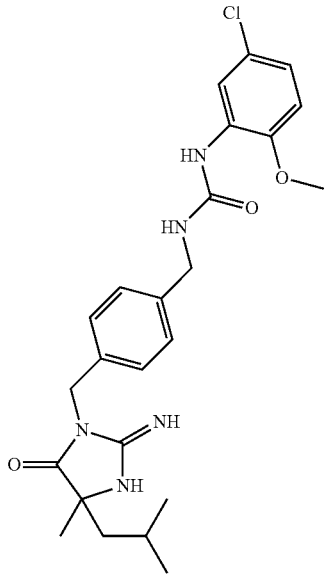
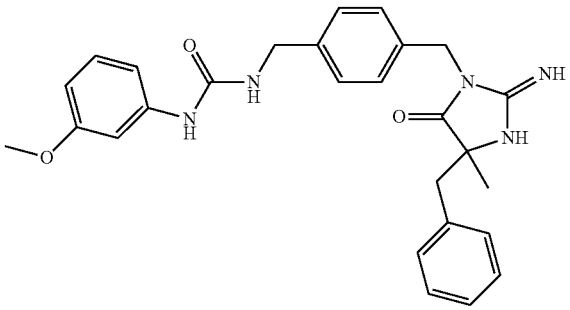
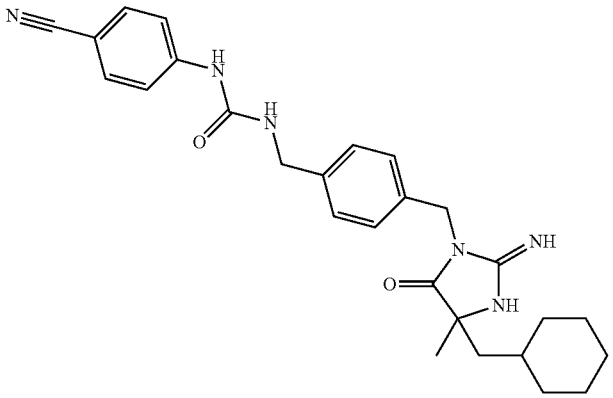
#	Structure	MW	Obs. m/e
880		471	472
881		471	472
882		472	473

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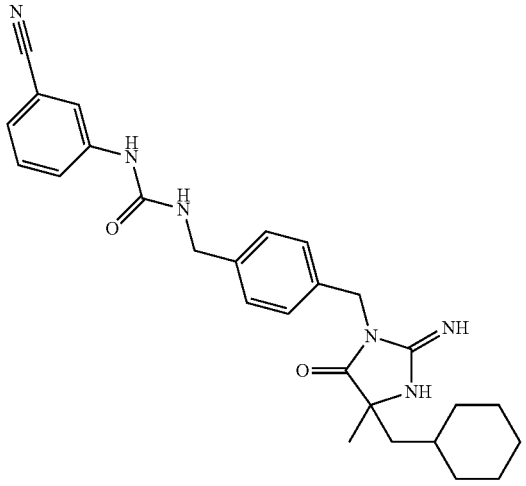
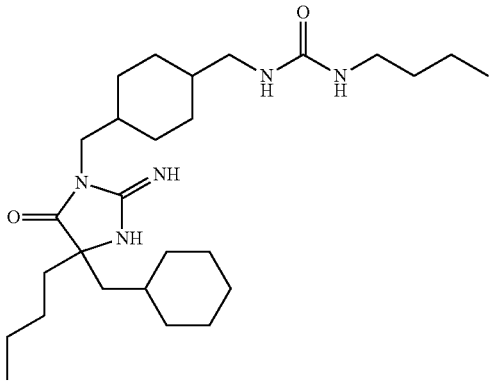
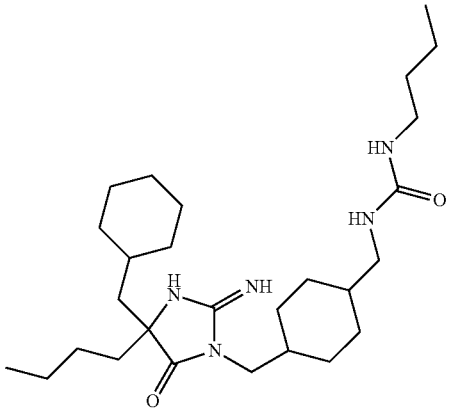
#	Structure	MW	Obs. m/e
883		472	473
884		475	476
885		475	476

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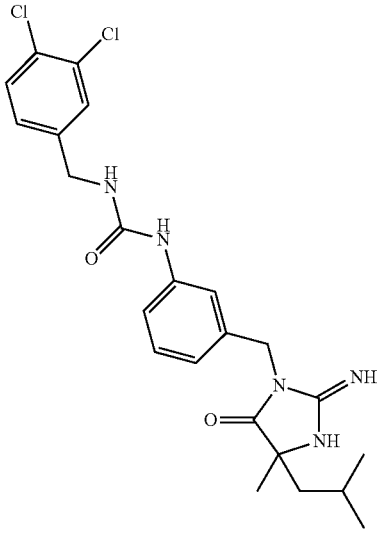
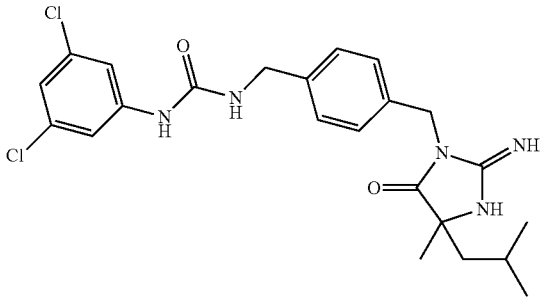
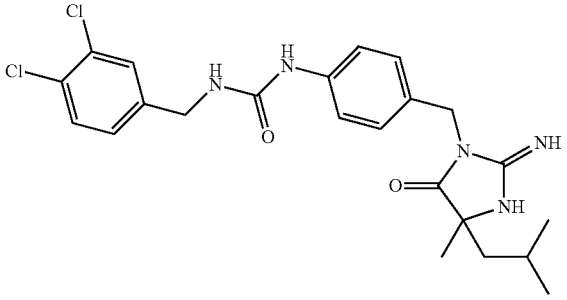
#	Structure	MW	Obs. m/e
886		475	476
887		475	476
888		475	476

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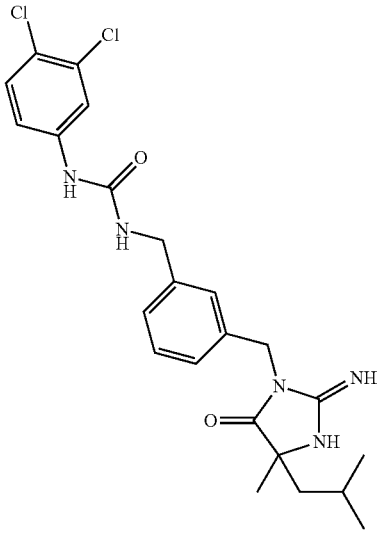
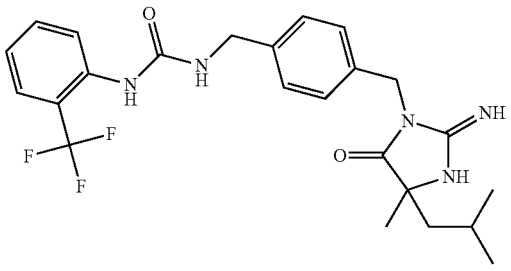
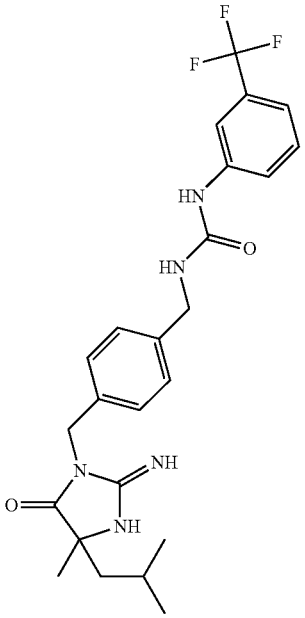
#	Structure	MW	Obs. m/e
889		475	476
890		475	476
891		475	476

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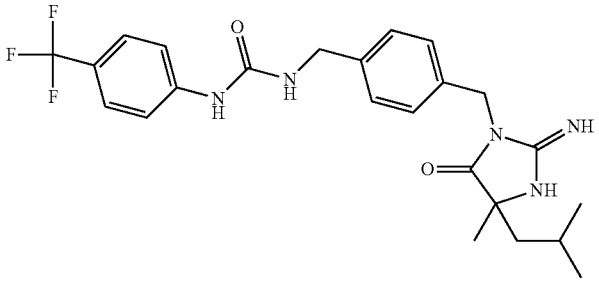
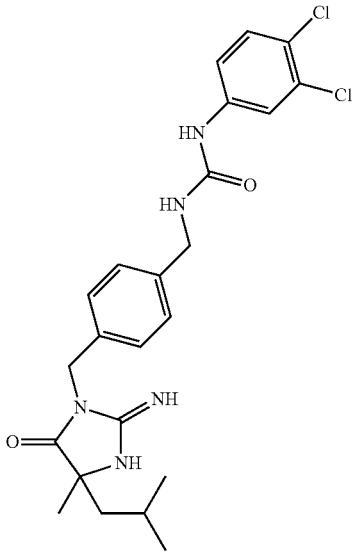
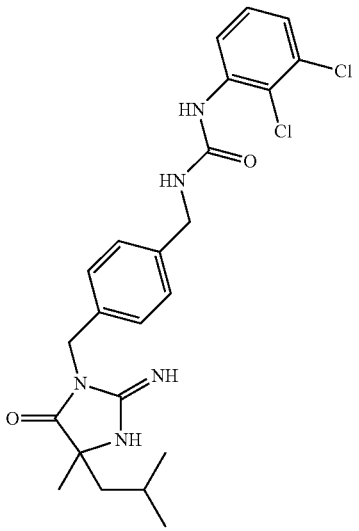
#	Structure	MW	Obs. m/e
892		475	476
893		475	476
894		475	476

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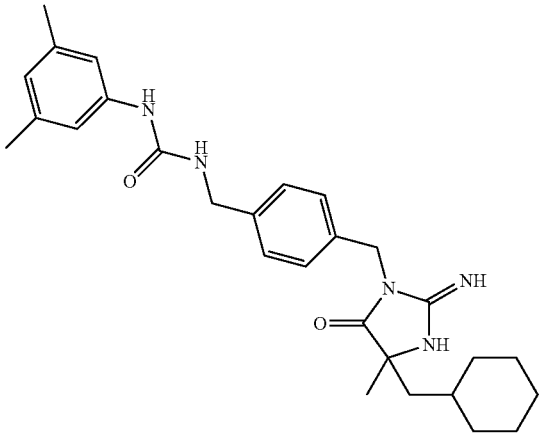
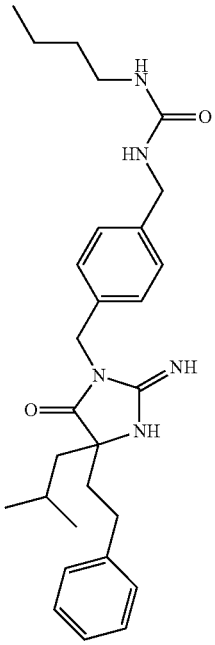
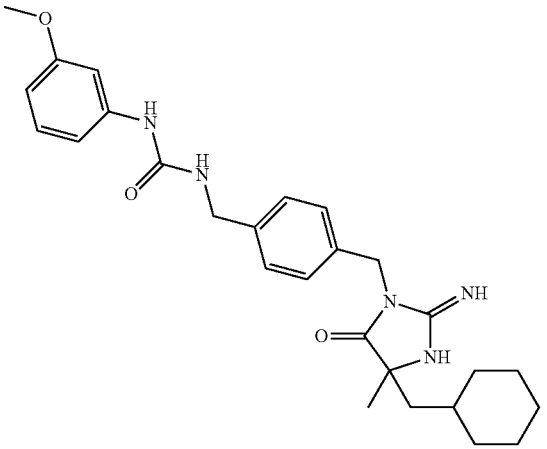
#	Structure	MW	Obs. m/e
895		475	476
896		477	478
897		477	478

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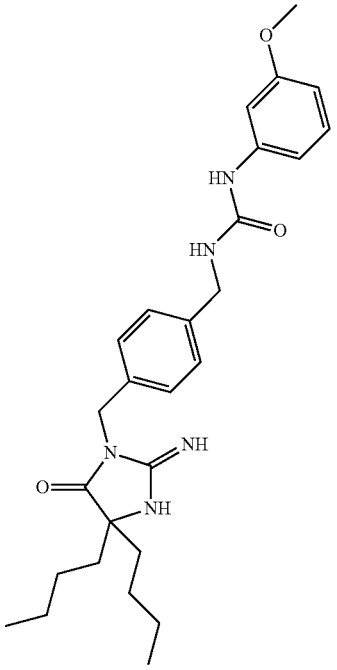
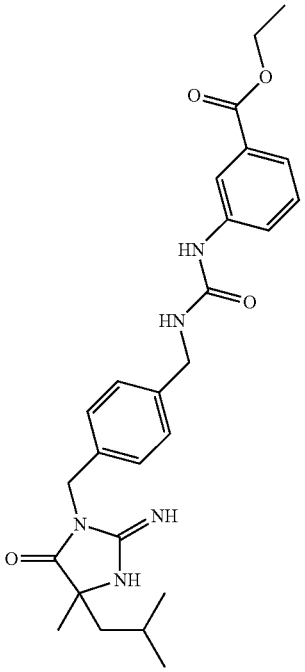
#	Structure	MW	Obs. m/e
898		479	480
899		479	480

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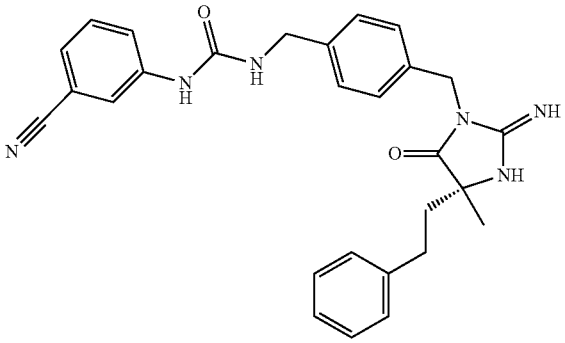
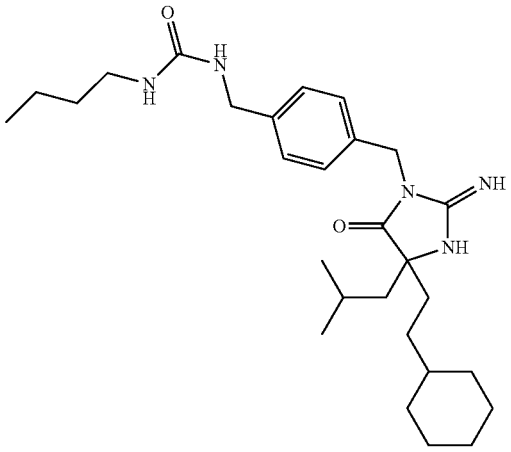
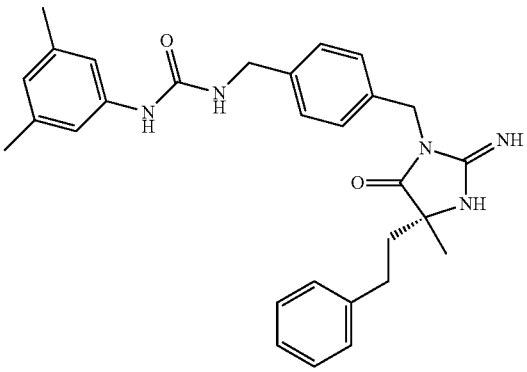
#	Structure	MW	Obs. m/e
900		480	481
901		483	484
902		483	484

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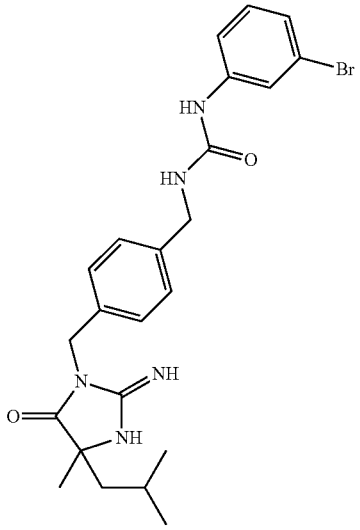
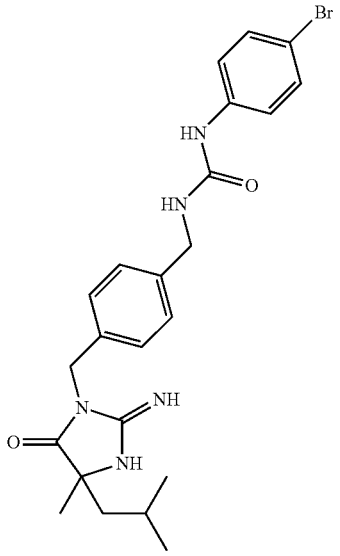
#	Structure	MW	Obs. m/e
903		485	486
904		485	486

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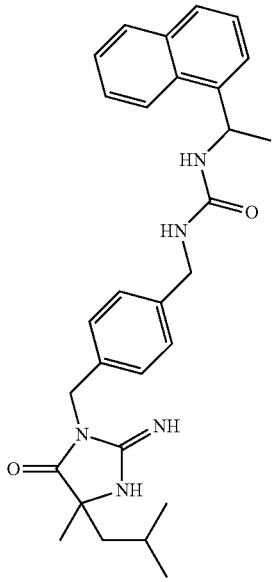
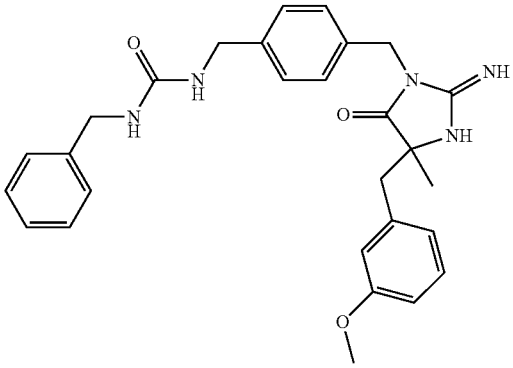
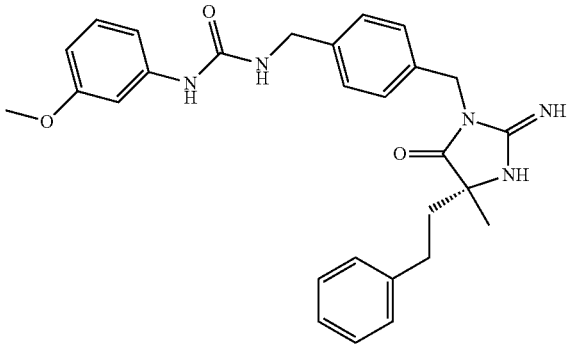
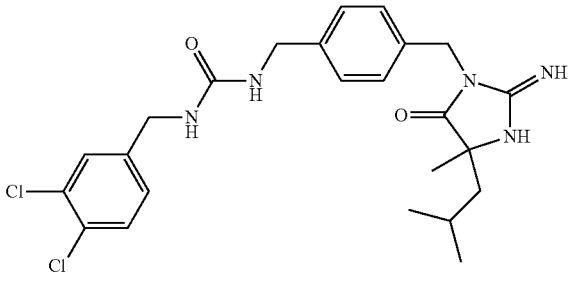
#	Structure	MW	Obs. m/e
905		485	486
906		485	486
907		485	486
908		489	490

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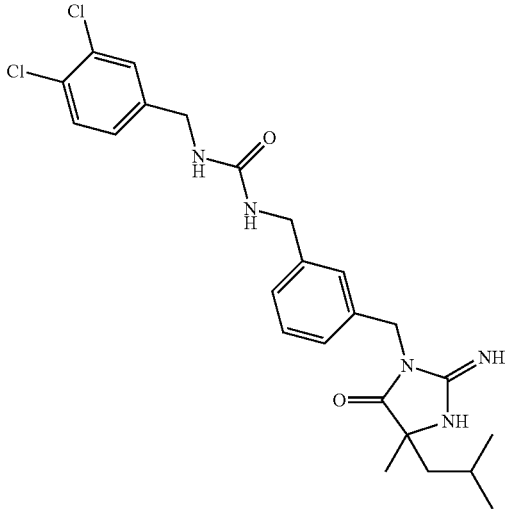
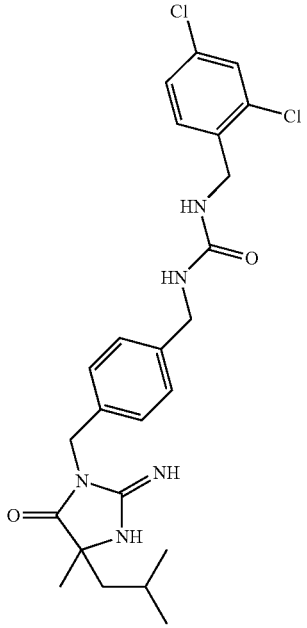
#	Structure	MW	Obs. m/e
909		489	490
910		489	490

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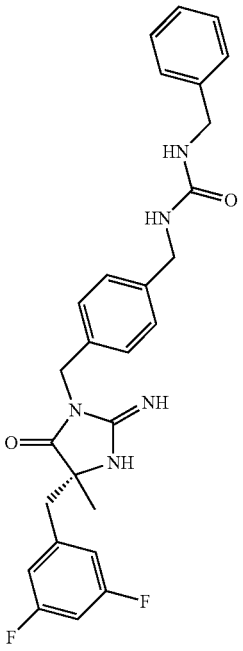
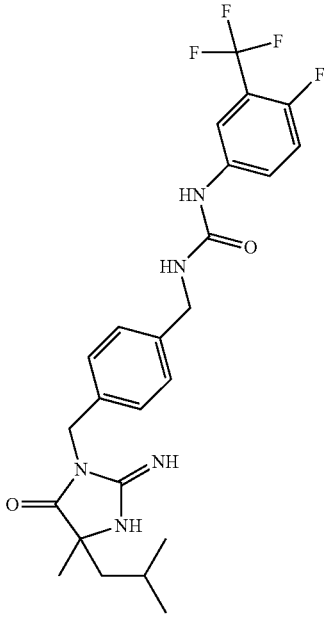
#	Structure	MW	Obs. m/e
911		491	492
912		493	494

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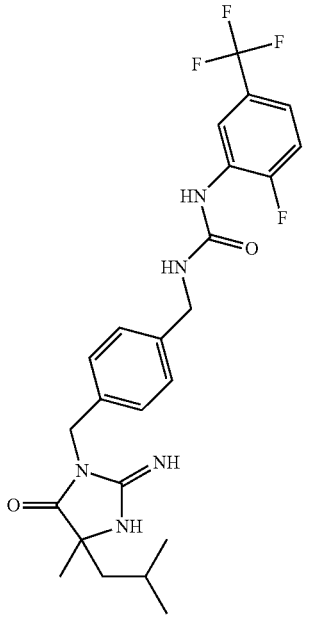
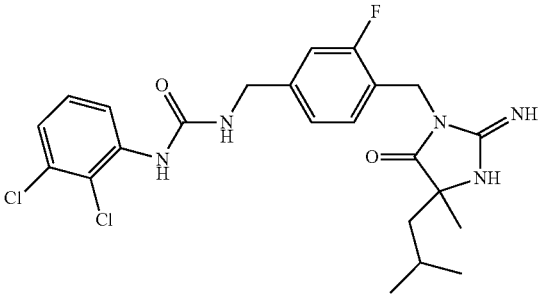
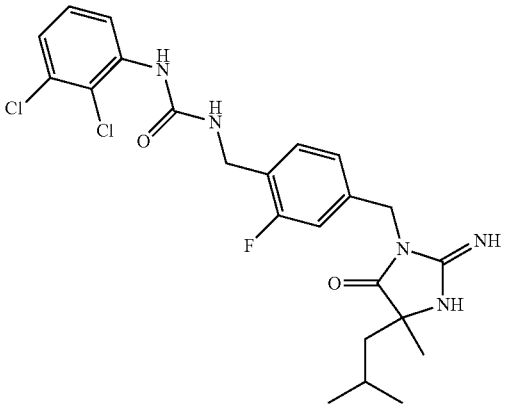
#	Structure	MW	Obs. m/e
913		493	494
914		493	494
915		493	494

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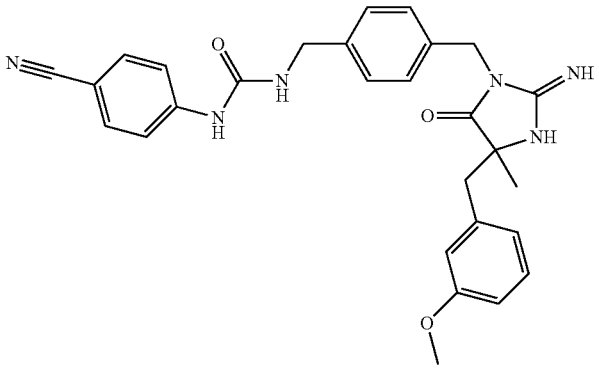
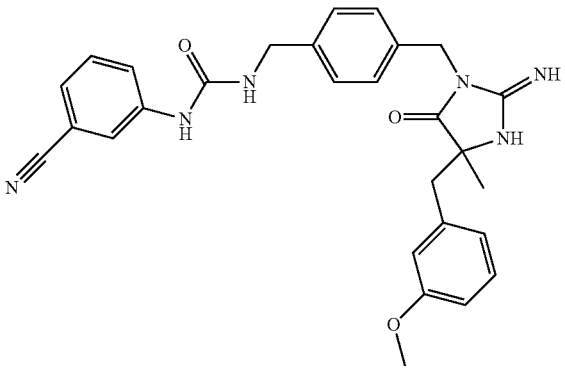
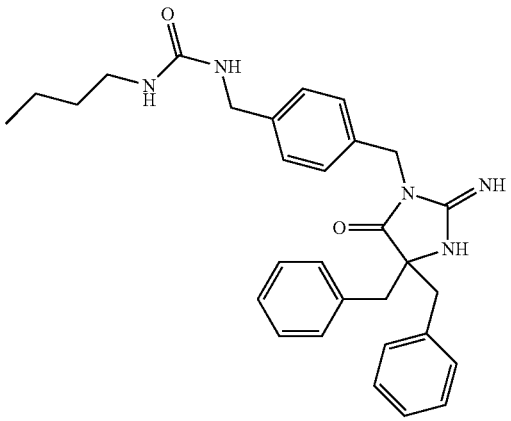
#	Structure	MW	Obs. m/e
916		496	497
917		496	497
918		497	498

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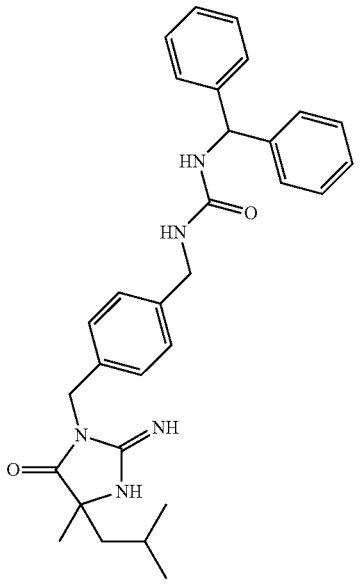
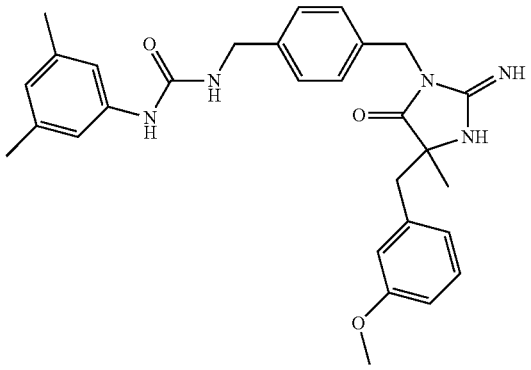
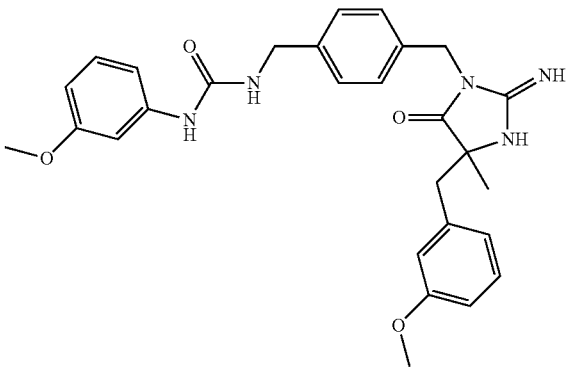
#	Structure	MW	Obs. m/e
919		497	498
920		499	500
921		501	502

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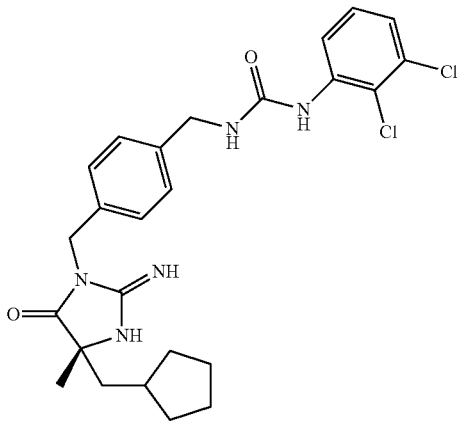
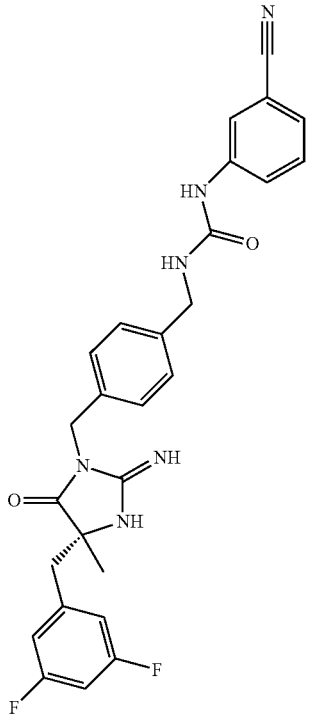
#	Structure	MW	Obs. m/e
922		501	502
923		502	503

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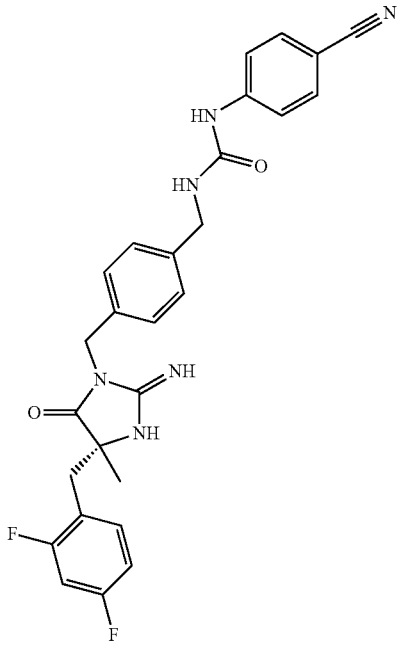
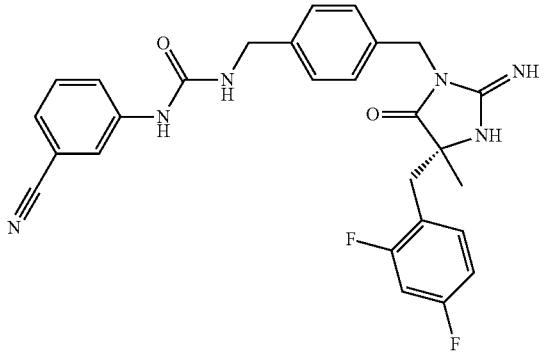
#	Structure	MW	Obs. m/e
924		502	503
925		502	503

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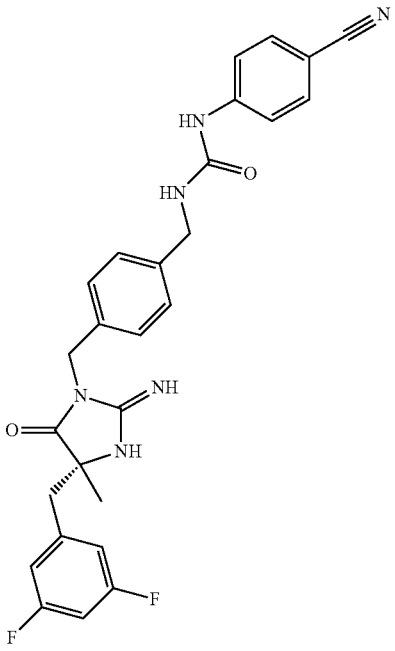
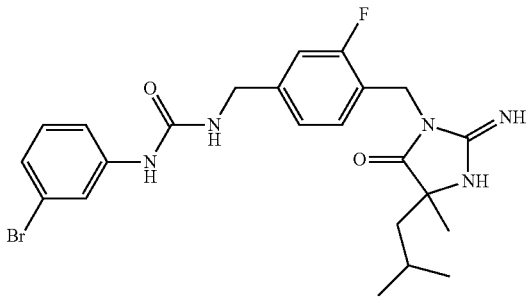
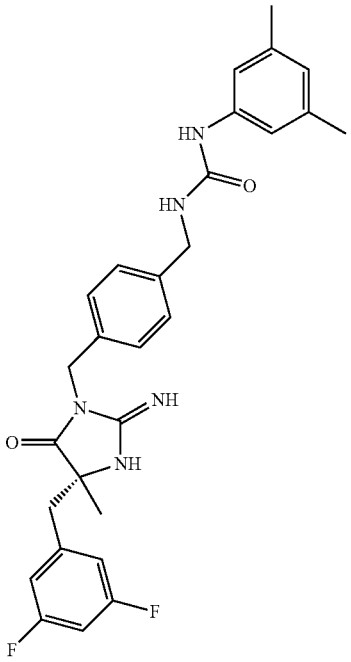
#	Structure	MW	Obs. m/e
926		502	503
927		503	504
928		505	506

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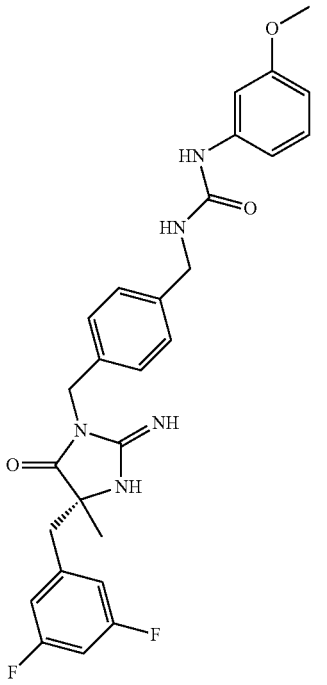
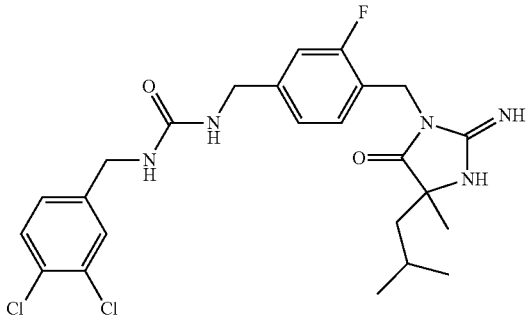
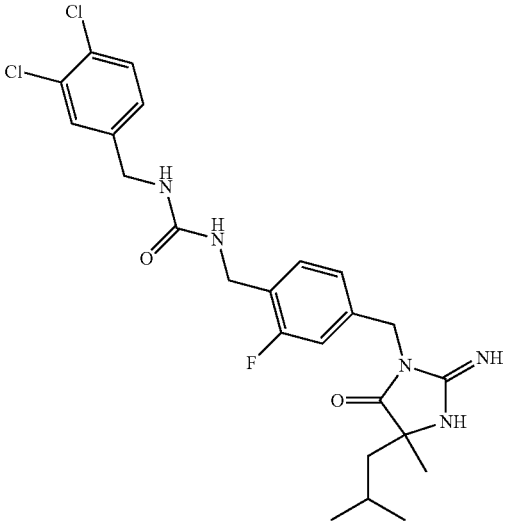
#	Structure	MW	Obs. m/e
929		507	508
930		507	508
931		507	508

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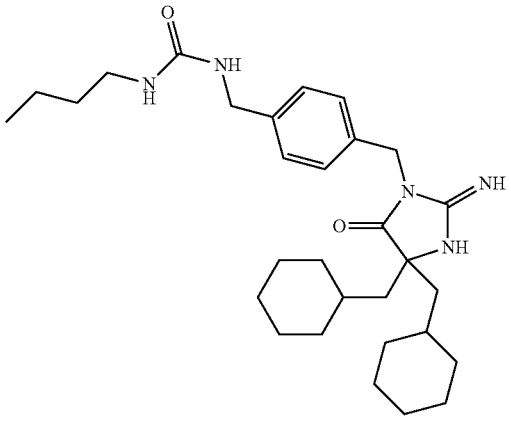
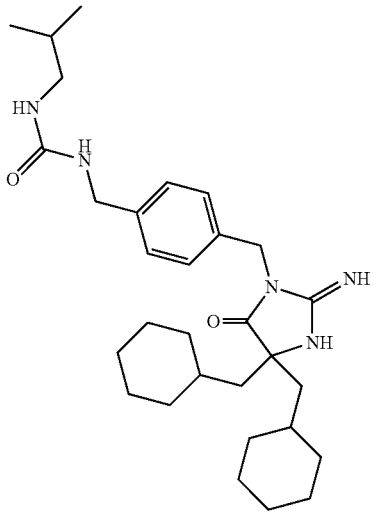
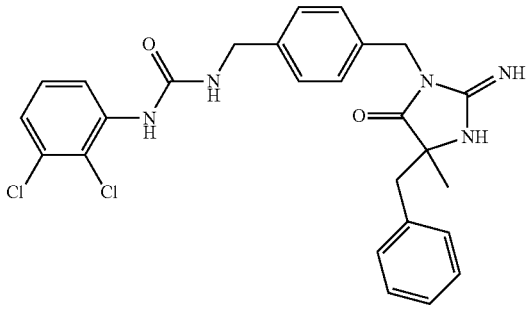
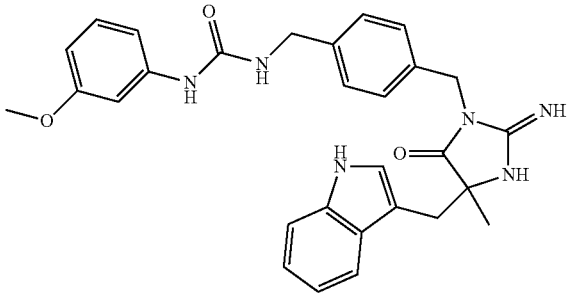
#	Structure	MW	Obs. m/e
932		509	510
933		509	510
934		509	510
935		510	511

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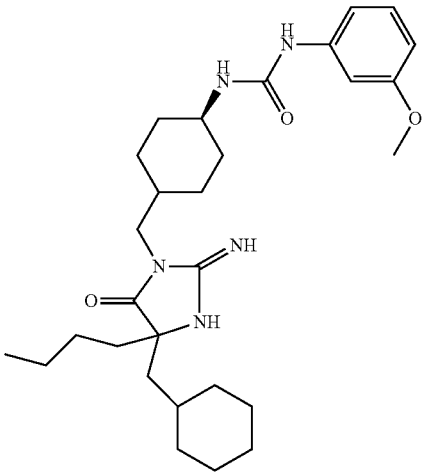
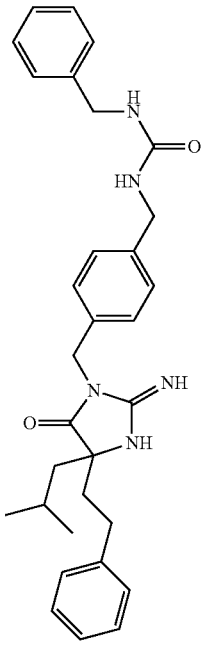
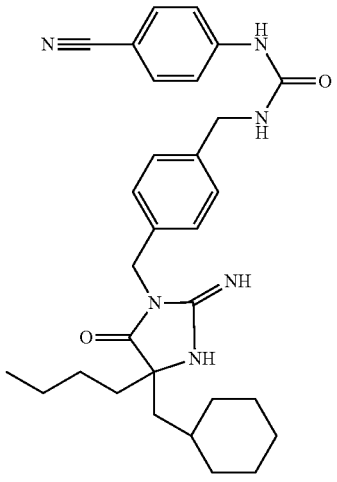
#	Structure	MW	Obs. m/e
936		511	512
937		511	512
938		514	515

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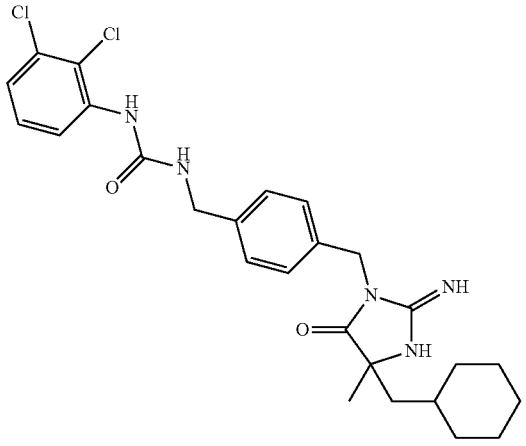
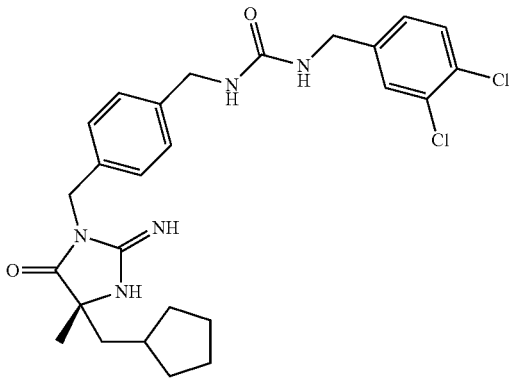
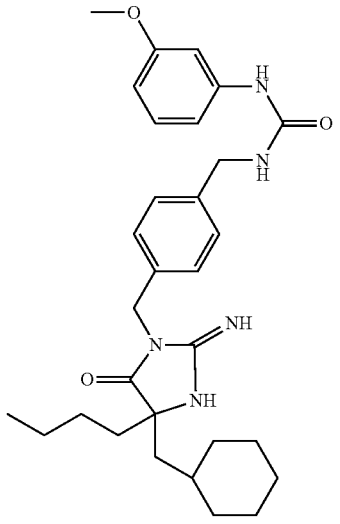
939		515	516
940		515	516
941		519	520

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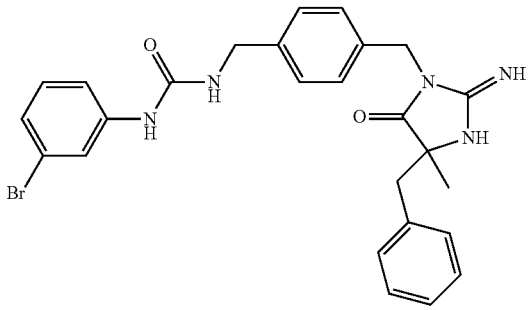
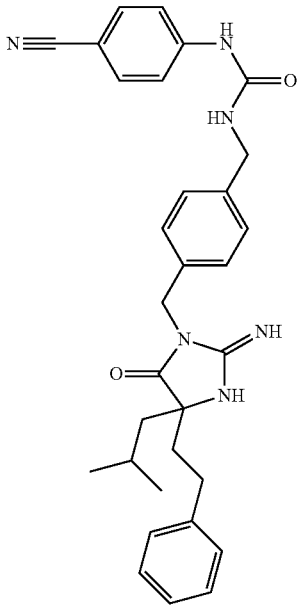
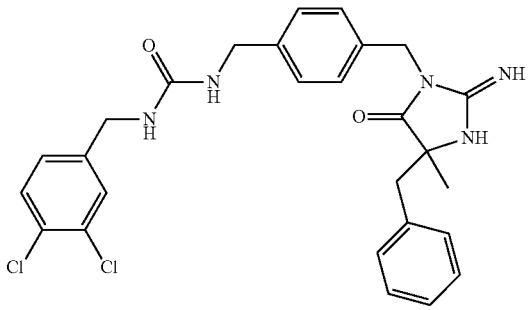
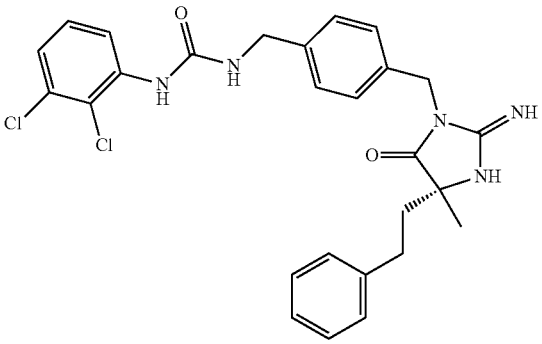
942		519	520
943		522	523
944		523	524
945		523	524

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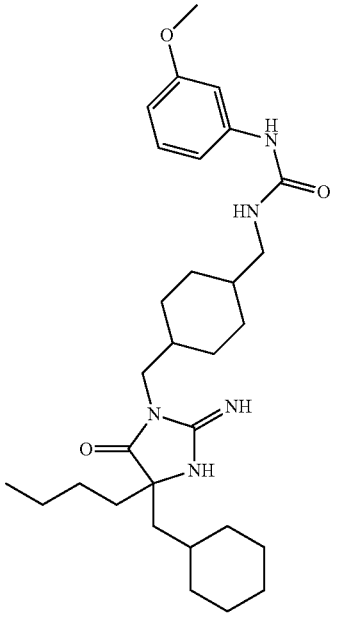
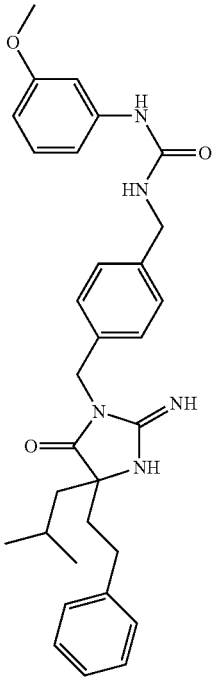
946		525	526
947		527	528

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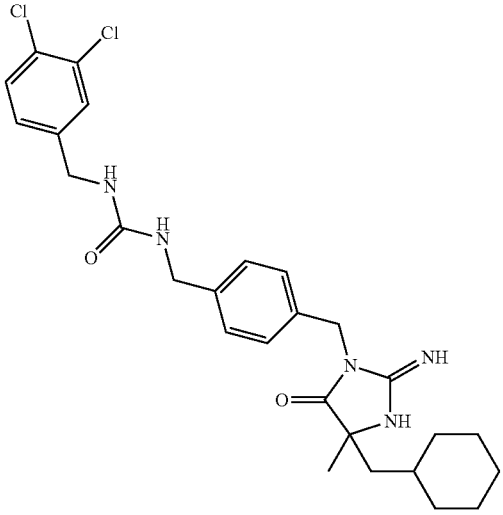
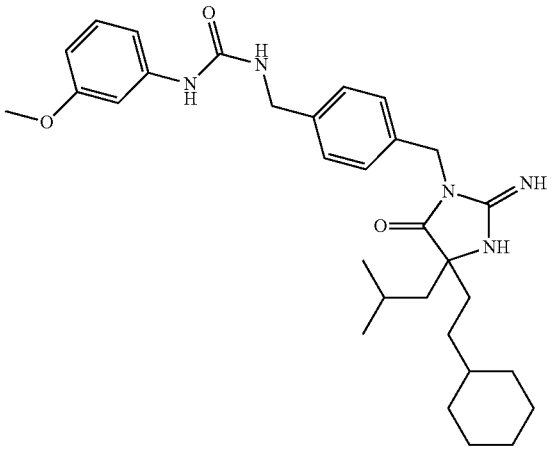
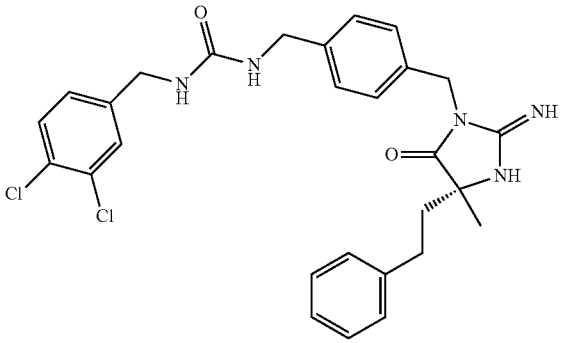
948		529	530
949		533	534
950		537	538

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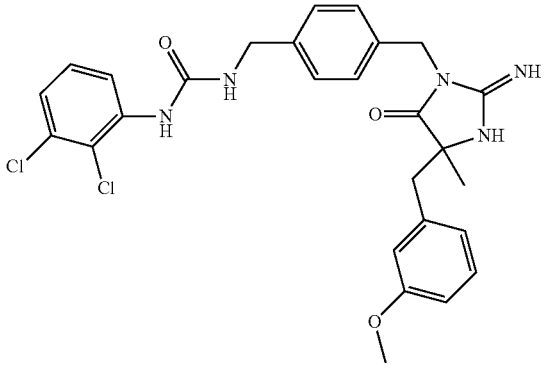
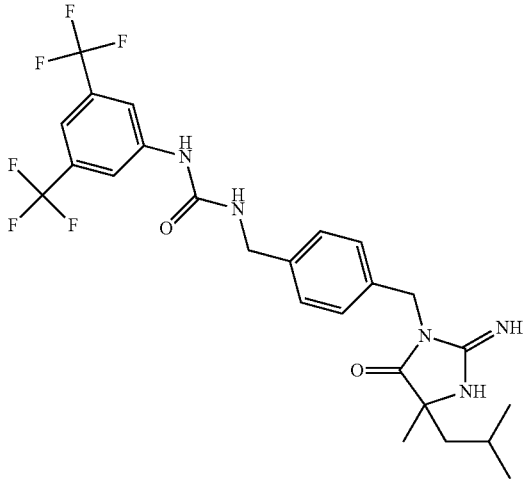
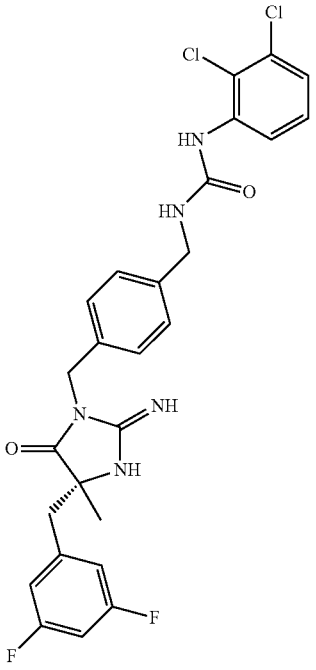
951		539	540
952		543	544
953		545	546

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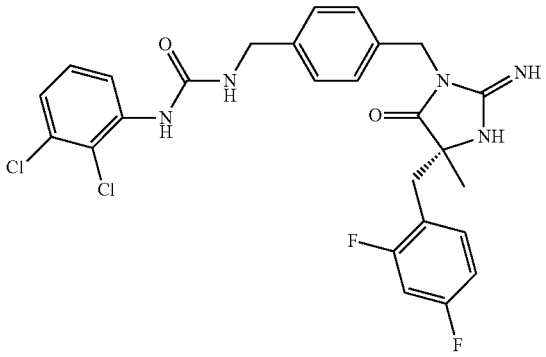
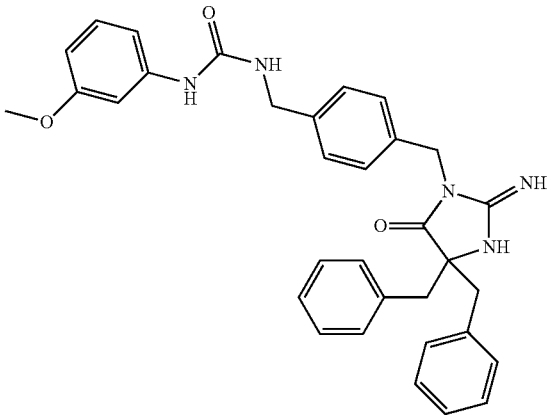
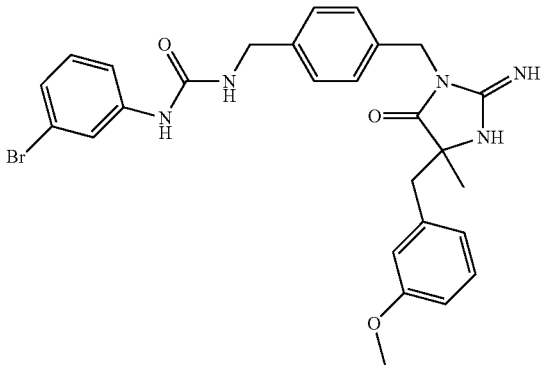
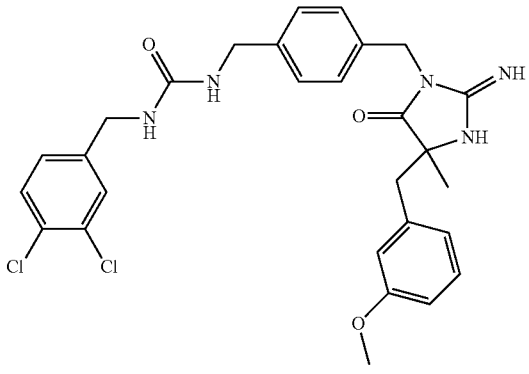
954		545	546
955		547	548
956		549	550
957		553	554

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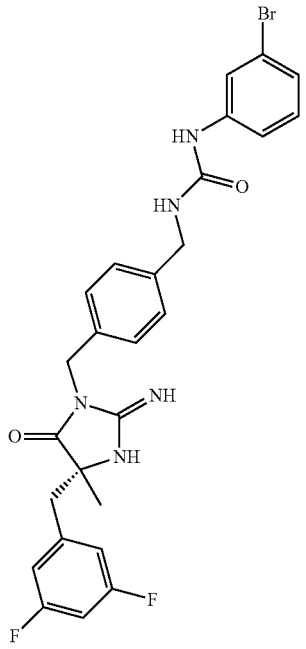
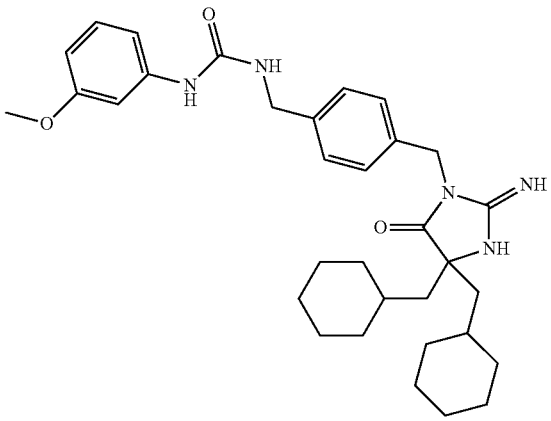
958		555	556
959		559	560

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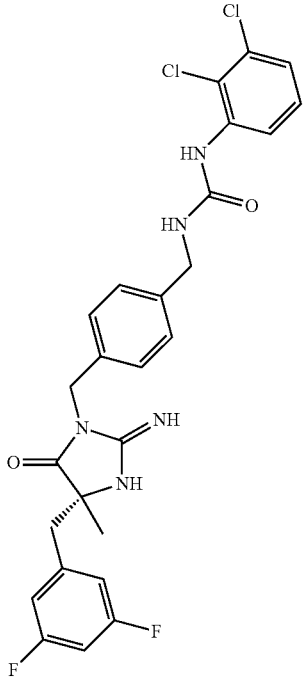
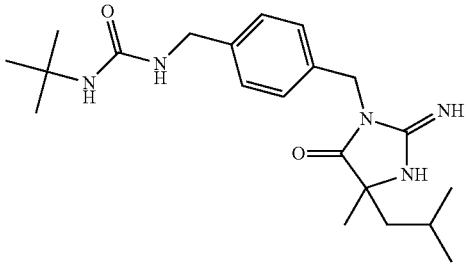
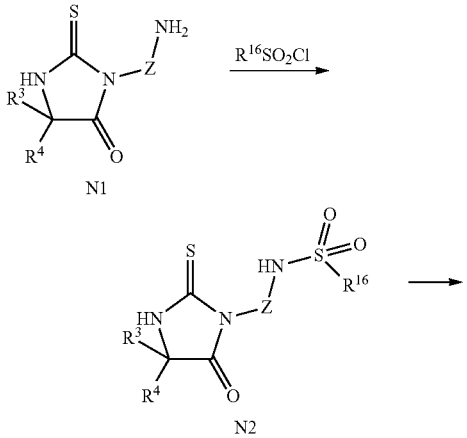
960		559	560
961		387	

Method N



N1

N2

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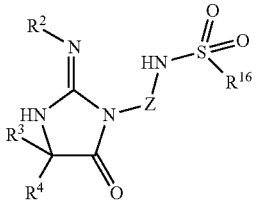


N3

(In the scheme, —Z—NH—$S(O)_2R^{16}$— is equivalent to R^1 substituted by R^{21}, or R^1 Substituted by alkyl-R^{22}, wherein R^{21} and R^{22} are —$N(R^{16})$—C(O)—NHR^{15} and R^{16} is H, and wherein Z is optionally substituted alkylene-arylenen, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

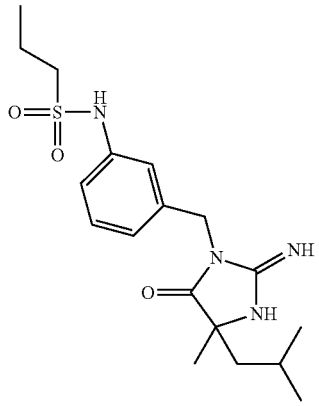
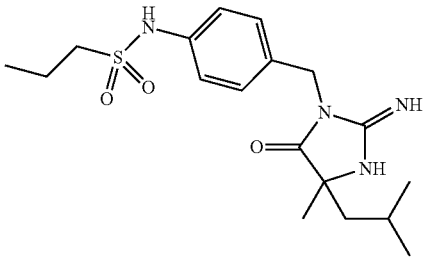
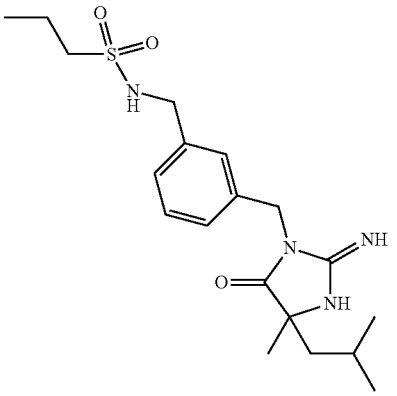
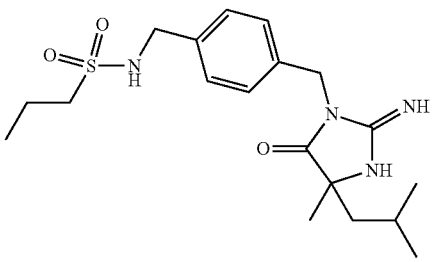
Method N, Step 1:

Compound N2 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—, R^{16}=$CH_2CH(CH_3)_2$) was prepared from N1 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—) following the procedure described in Method K, Step 1.

Method N, Step 2:

Compound N3 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—, R^{16}=$CH_2CH(CH_3)_2$) was prepared from N2 (R^3=CH_3, R^4=$CH_2CH(CH_3)_2$, Z=para-$(CH_2)C_6H_4(CH_2)$—, R^{16}=$CH_2CH(CH_3)_2$) following the procedure described in Method A, Step 3.

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e
962		380	381
963		380	381
964		394	395
965		394	395

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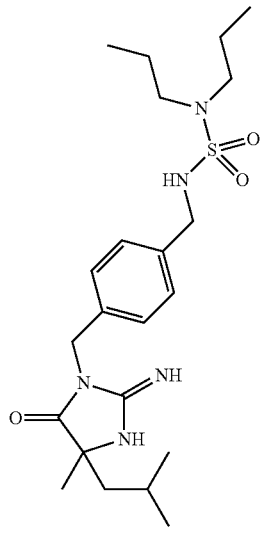
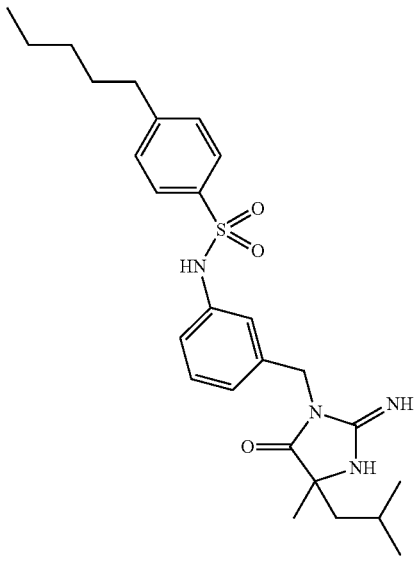
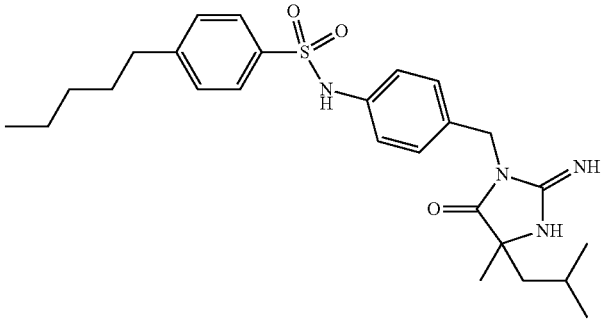
#	Structure	MW	Obs. m/e
966		451	452
967		484	485
968		484	485

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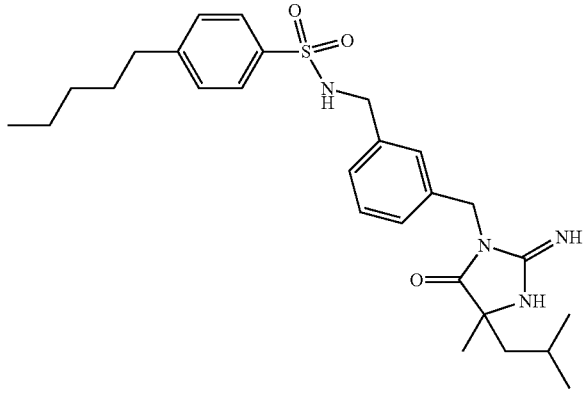
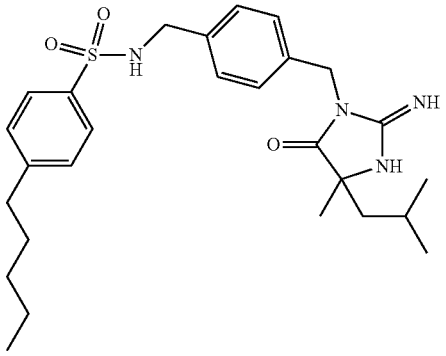
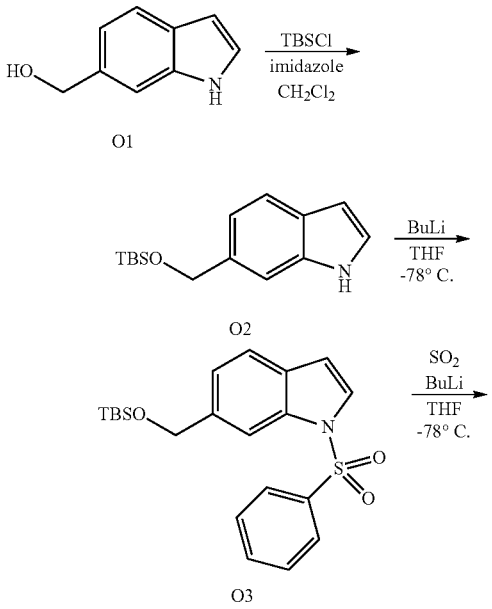
969		498	499
970		498	499

Method O



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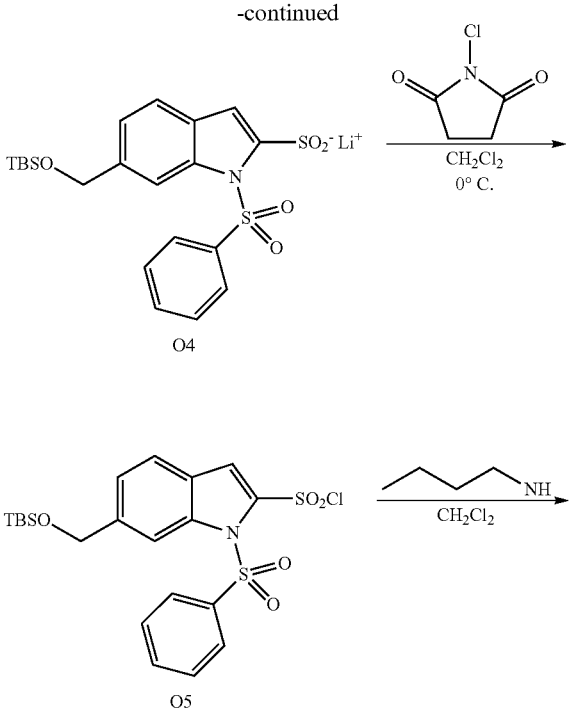

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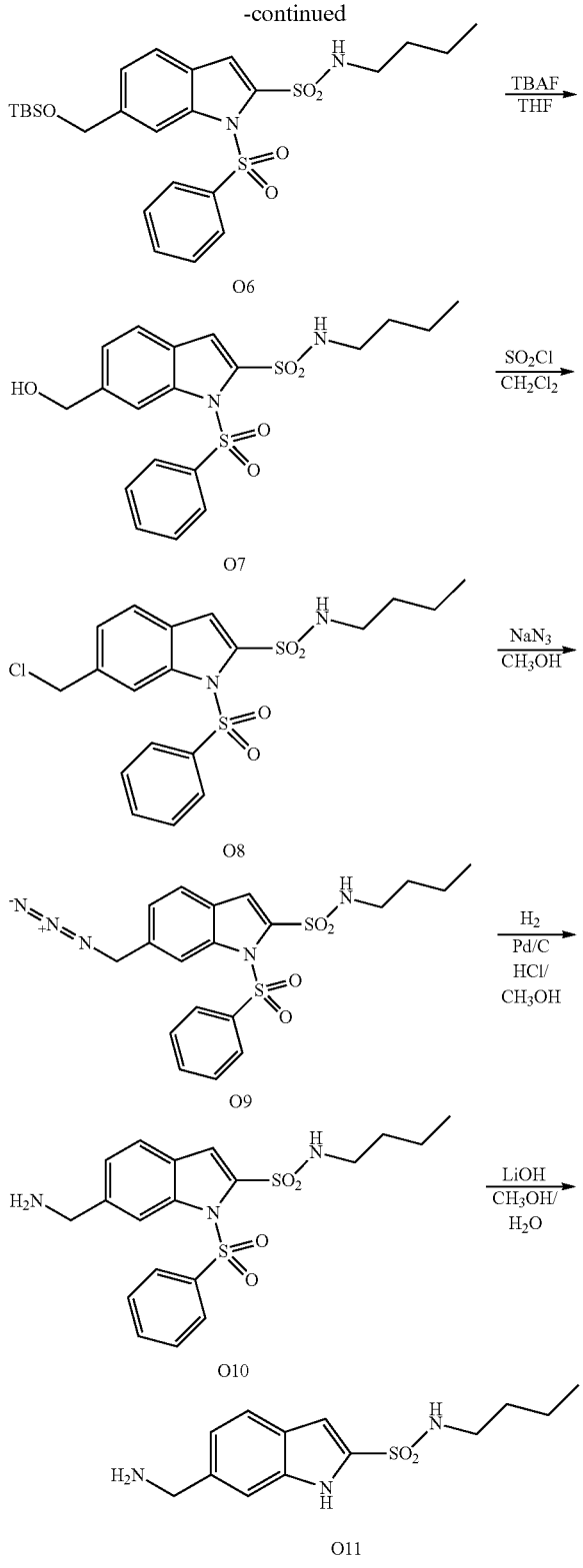


Method O, Step 1:

A solution of indole-6-methanol (400 mg, 2.72 mmol), tert-butyldimethylsilyl chloride (816 mg, 5.41 mmol) and imidazole (740 mg, 10.9 mmol) in CH_2Cl_2 was stirred at rt. overnight before the solvent was evaporated and residue chromatographed using ethylacetate/hexane to give product O2.

Method O, Step 2:

To a solution of O2 (200 mg, 0.77 mmol) in THF (10 mL) at −78° C. was added butyl lithium (1.2 eq). The solution was stirred at −78° C. for 5 min and then warmed to rt. The reaction mixture was cooled to −78° C. and p-toluenesulfonyl chloride was added. The solution was warmed to rt and stirred overnight. The reaction was quenched with a saturated aqueous K_2CO_3 solution, extracted with ethyl acetate and CH_2Cl_2. The crude material was purified via flash chromatography using ethylacetate/hexane to afford 360 mg of O3.

Method O, Step 3:

A solution butyl lithium (1.2 eq) was added to a solution of O3 (340 mg, 0.829 mmol) in THF (20 mL). The reaction mixture was stirred for 15 min at −78° C. then sulfur dioxide was bubbled through the solution for 15 min. Hexane (100 mL) was added to the reaction mixture. The reaction mixture was evaporated to afford O4 which was used in the next step without further purification.

Method O, Step 4:

To a solution of O4 (0.829 mmol) in CH_2Cl_2 cooled to 0° C. was added N-chlorosuccinimide (220 mg, 1.66 mmol). After 2 h of stirring, the solution was filtered through a Celite plug. The filtrate was concentrated to afford O5.

Method O, Step 5:

To a solution of O5 in anhydrous pyridine (3 mL) was added butyl amine (100 μL). The reaction was agitated at rt for 4 d. The reaction mixture was partitioned between 1 N HCl and CH_2Cl_2. The organic layer was separated and washed with 1 N HCl (3×). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography using ethylacetate/hexane to yield O6.

Method O, Step 6:

To a solution of O6 (70 mg) in THF was added TBAF. The reaction was stirred at rt. before the reaction mixture was chromatographed using ethylacetate/hexane to afforded 50 mg of O7 (95%).

Method O, Step 7:

To a solution of O7 (50 mg) in CH_2Cl_2 (5 mL) was added thionyl chloride (1 mL) the reaction was stirred for 5 min and then evaporated to afford O8.

Method O, Step 8:

To a solution of O8 in CH_3OH (5 mL) was added sodium azide (50 mg). The solution was stirred at rt overnight and solvent evaporated. The residue was chromatographed using ethylacetate/hexane to afforded O9 after purification.

Method O, Step 9:

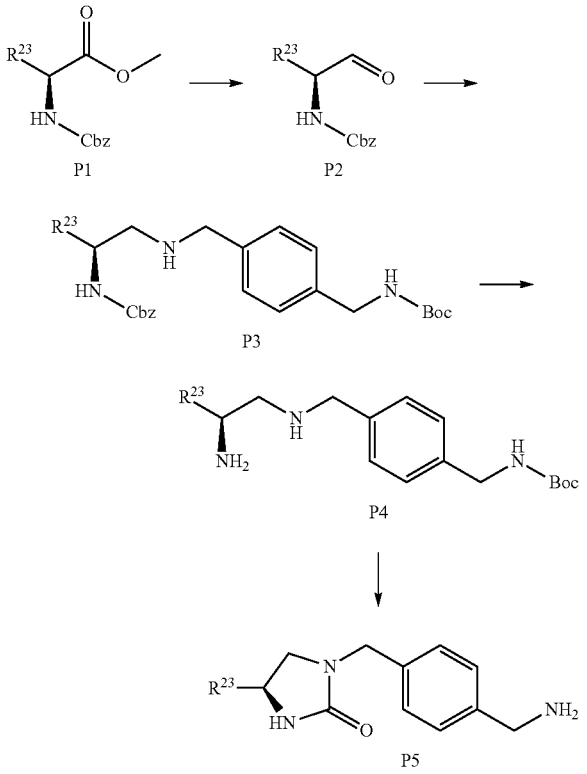
To a suspension of O9 (70 mg) in CH_3OH was added 1 eq HCl (aq) and palladium on carbon. The reaction mixture was hydrogenated at 1 atm for 20 min to yield 90 mg of crude product O10.

Method O, Step 10:

A solution of lithium hydroxide (30 mg) in H_2O was added to a solution of O10 (40 mg) in CH_3OH (3 mL). The reaction was stirred at rt for 2 h and an additional portion of LiOH (40 mg) was added and solution was stirred for 2 more hours. The

solvent was evaporated and residue chromatographed using ethylacetate/hexane to afforded O11.

Method P



Method P, Step 1:

A 300 mL of THF solution of 100 g of P1 (R^{23}=n-Pr) was added to a suspension of 38 g of LAH in 2 L of anhydrous THF at 0 C. The reaction mixture is stirred at r.t. for 1 h before 30 ml of H_2O, 90 ml of 15% NaOH was added at 0° C. The mixture was stirred at r.t. for one hour before Na_2SO_4 (anh) was added, the mixture was filtered, and the solution evaporated to give a product which was dried under vacuo overnight. This product was dissolved in 600 ml of DCM and the solution was added into a solution of oxalyl chloride (37.3 ml) and DMSO (60.8 ml) in 1.4 L of DCM at −78° C. over 40 min before Diisopropylethylamine (299 ml) was added at −78° C. The reaction was allowed to reach −10° C. The reaction was quenched with 1 L H_2O at −10° C. and the mixture was extracted with DCM. After removal of solvent, P2 (R^{23}=Pr, 106 g) was obtained. The crude material was used for next step without purification.

Method P, Step 2:

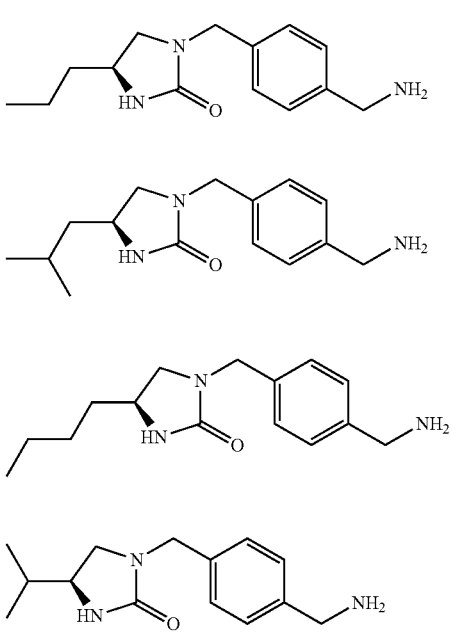
To a 1.5 L DCM solution of P2 (R^{23}=Pr, 106 g) was added p-Boc-aminomethylbenzylamine (1.1 eq) and sodium triacetoxyborohydride (1.1 eq) and the reaction was stirred at r.t. overnight. The reaction was quenched with H_2O and content extracted with DCM. After removal of solvents the residue was chromatographed using a silica gel column eluted with 3% MeOH in DCM to give 42.5 g of P3 (R^{23}=Pr).

Method P, Step 3:

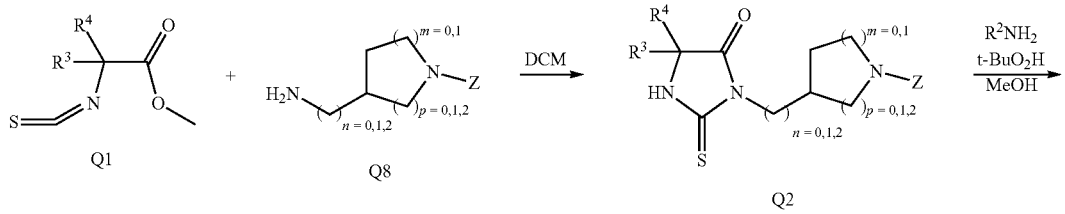
A 10 ml MeOH solution of P3 (R^{23}=Pr, 110 mg) was hydrogenated using Pd/C (5%, 11 mg) at 1 atm of hydrogen to give product P4 (R^{23}=Pr) after removal of solvent and catalyst.

Method P, Step 4:

To a 10 ml DCM solution of P4 at 0° C. (R_{23}=Pr) was added triphosgene (1.2 eq) and triethylamine (2.4 eq) and the solution was stirred at 0 C for 2 h before the reaction was extracted with DCM/H2O. After removal of the solvent, the residue was chromatographed using a silica gel column eluted with EtOAc/Hexane to give a white solid which was treated with 2N HCl in dioxane for 2 h. After removal of the solvent, compound P5 (R^{23}=Pr) as a white solid was obtained (80 mg). The following compounds were synthesized using similar methods:



Method Q



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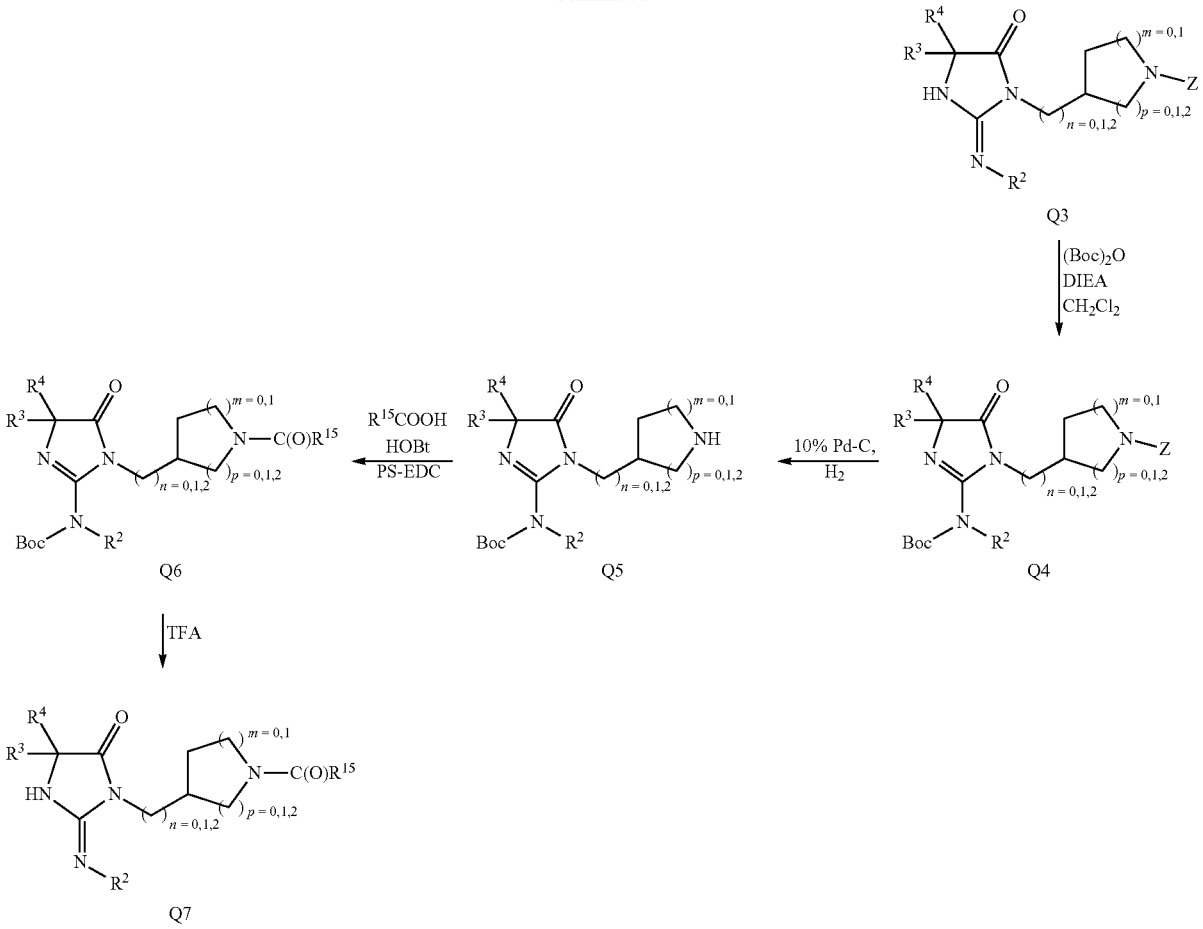

Method Q, Step 1

At room temperature, Q1 (R^3=Me; R^4=iBu) (1.00 g) and Q8 (n=1, p=2, m=1) (1.24 g) in dichloromethane (30 mL) were stirred for 42 h. This mixture was concentrated in vacuo to give an amber oil which was purified on a column of silica gel (200 mL) eluted with ethylacetate/hexane to give Q2 (n=1, p=2, m=1, R^3=Me; R^4=iBu), a colorless oil (1.59 g).

Method Q, Step 2

Compound Q3 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=iBu) was prepared from Q2 (n=1, p=2, m=1, R^3=Me; R^4=iBu) using method similar to method A step 3.

Method Q, Step 3

Compound Q3 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=iBu) (1.37 g) in anhydrous dichloromethane (25 mL) was treated with di-tert-butyl dicarbonate (0.68 g, 1.1 equiv.) and diisopropylethylamine (0.66 mL, 1.1.equiv.). The resulting solution was stirred at room temperature for 20 h before it was diluted with dichloromethane and washed with 1N hydrochloric acid. The dried dichloromethane solution was concentrated in vacuo to give a colorless film (1.32 g) which was purified on a column of silica gel (125 mL) and eluted with hexane:ethyl acetate to give compound Q4 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=i-Bu) as a white foam (0.74 g).

Method Q, Step 4

Compound Q4 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu) (0.540 g) in absolute EtOH (20 mL) was hydrogenated with 10% Pd/C (0.400 g) at 1 atm for 2 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo to give Q5 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu) as a colorless oil (0.35 g).

Method Q, Step 5

Compound Q5 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=iBu) (0.012 g) and HOBt (0.005 g) dissolved in acetonitrile (0.8 mL) and tetrahydrofuran (0.25 mL) was treated with EDC resin (0.080 g, 3 eq., 1.53 mmol/g) in a microtiter plate well followed by addition of a 1M dichloroethane solution (40 uL, 125 eq.). After the well was capped and shaken for 18 h, the mixture was filtered and the resin washed with acetonitrile (0.5 mL). The combined solution was treated with Trisamine resin (0.050 g, 6 eq., 4.23 mmol/g) and Isocyanate resin (0.067 g, 3 eq., 1.53 mmol/g) for 18 h before the solution was filtered and the solvent was removed in vacuo to give Q6 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu, R^{15}=Me).

Method Q, Step 6.

A dichloromethane solution (1.0 mL) of Q6 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu, R^{16}=Me) was mixed with trifluoroacetic acid (1.0 mL) and the solution was shaken for 2 h before it was concentrated. Diethyl ether (0.5 mL) was added and then concentrated in vacuo to give a residue, which was purified on a Prep LCMS unit to give Q7 (=1, p=2, m=1, R2=H, R_3=Me; R_4=iBu, R_{15}=Me). NMR ($CDCl_3$): δ 8.38, br, 2H; δ 4.56, m, 1H; δ 3.79, m, 1H; δ 3.57, m, 2H; δ 2.99, m, 1H; δ 2.48, m, 1H; δ 2.04, 5, 3H; δ 1.95, m, 1H; δ 1.5-1.8, m, 5H; δ 1.5, s, 3H; 1.25, m, 2H; δ 0.95, m, 3H; δ 0.85, m, 3H. ES_LCMS (m/e) 309.17.

The following compounds were prepared using similar methods:

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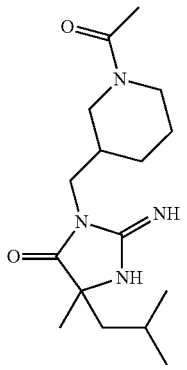
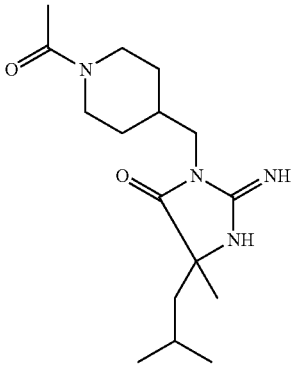
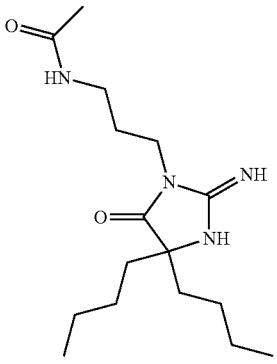
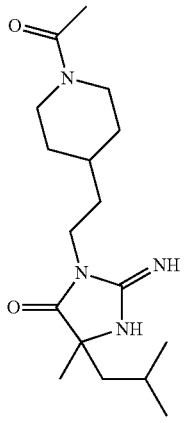
971		308	309
972		308	309
973		310	311
974		322	323

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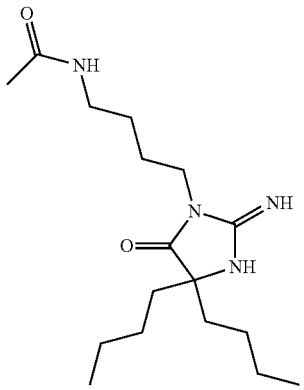
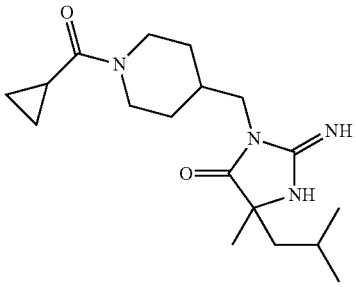
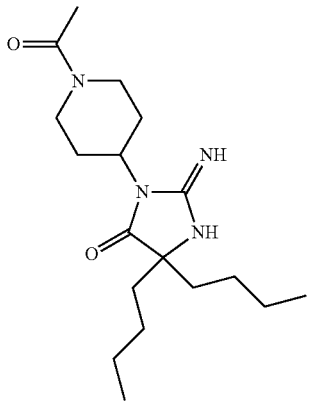
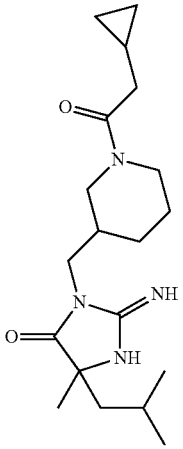
975		324	325
976		334	335
977		336	337
978		348	349

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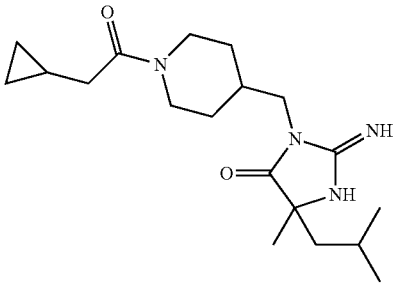
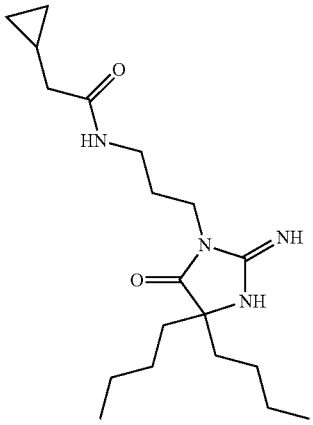
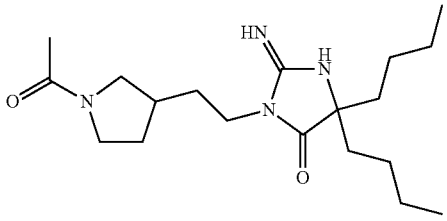
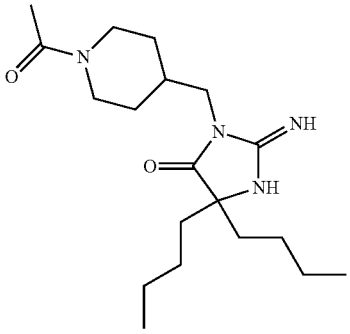
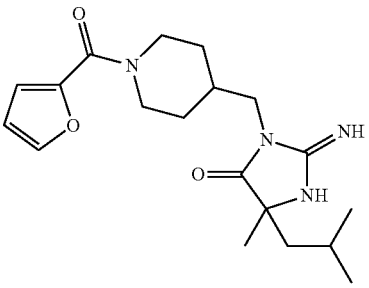
979		348	349
980		0	351
981		350	351
982		350	351
983		360	361

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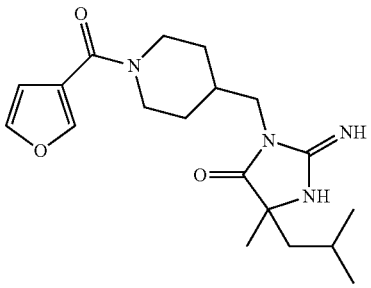
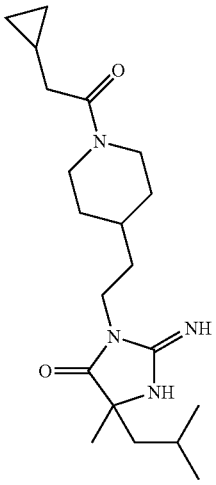
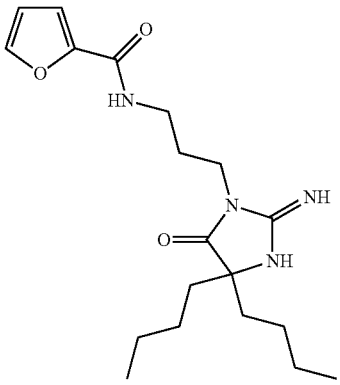
984		360	361
985		362	363
986		362	363

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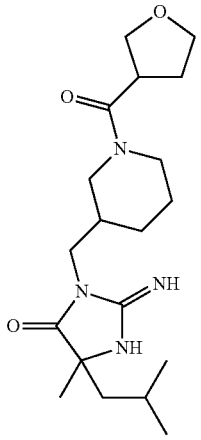
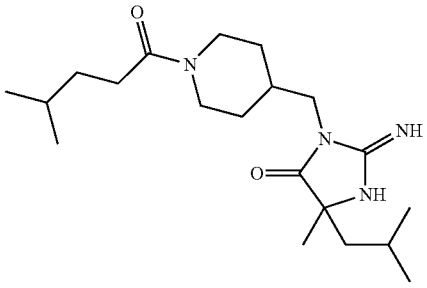
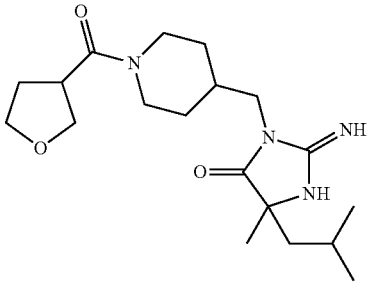
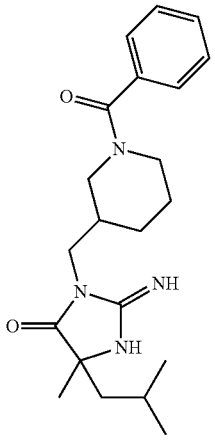
987		364	365
988		364	365
989		364	365
990		370	371

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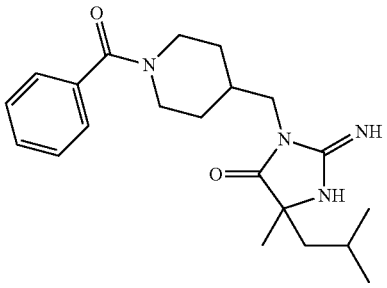
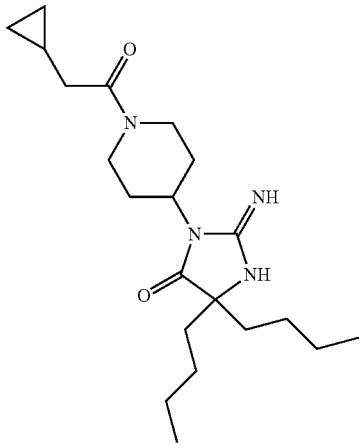
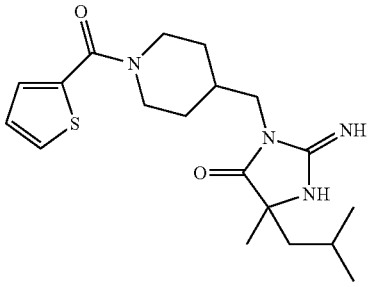
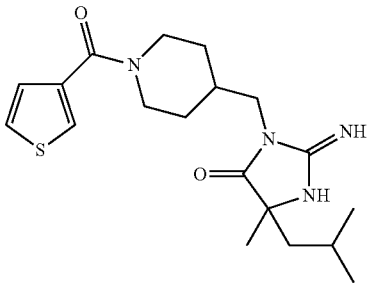
991		370	371
992		376	377
993		376	377
994		376	377

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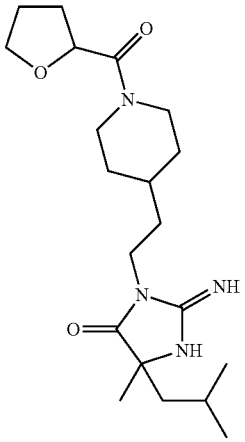
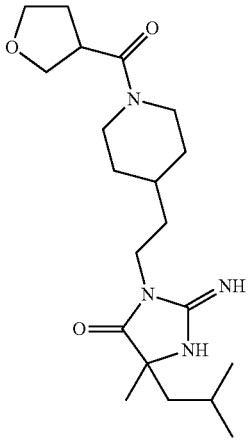
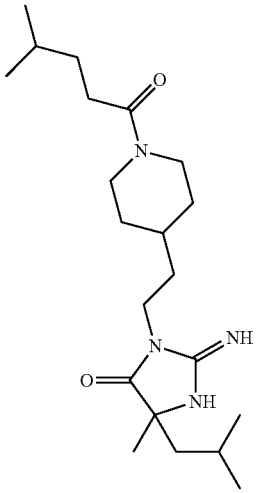
995		378	379
996		378	379
997		378	379

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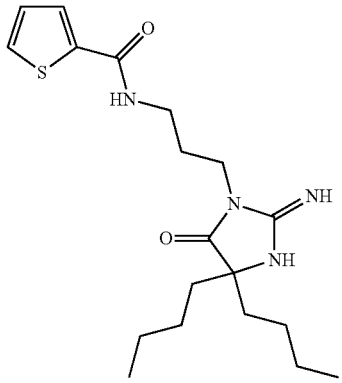
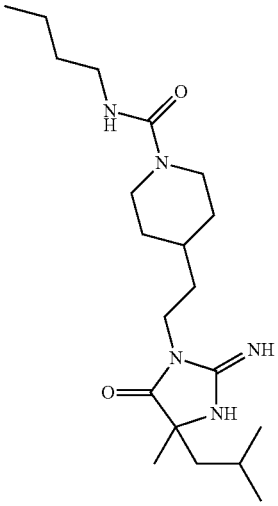
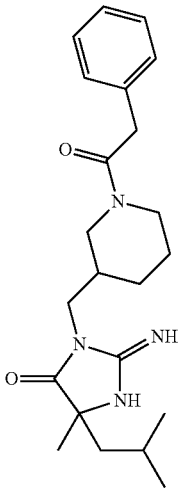
998		378	379
999		379	380
1000		384	385

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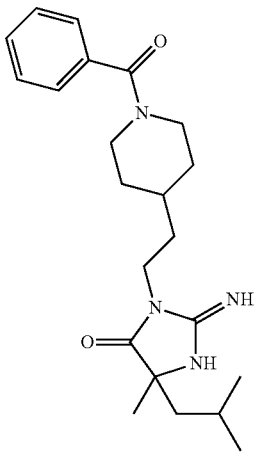
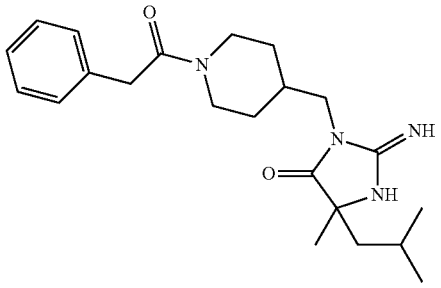
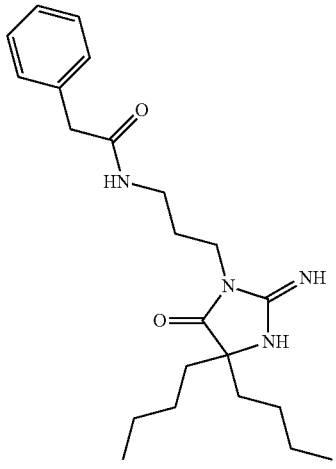
1001		384	385
1002		384	385
1003		386	387

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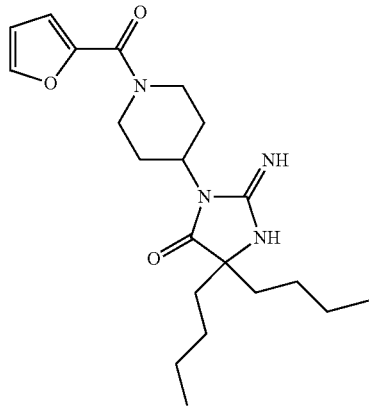
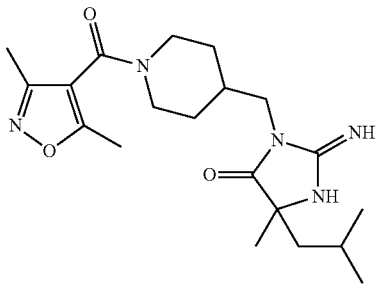
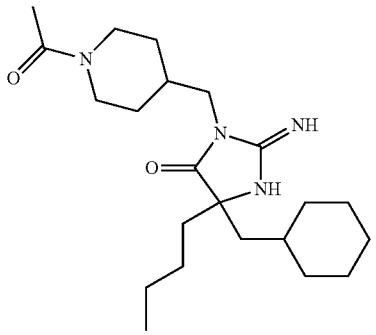
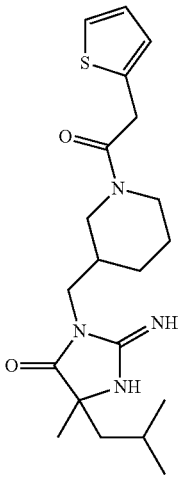
#	Structure	MW	Obs. m/e
1004		388	389
1005		389	390
1006		390	391
1007		390	391

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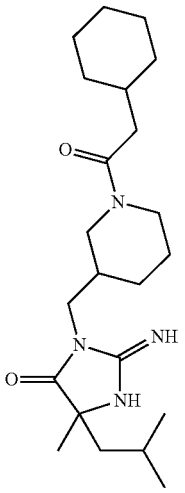
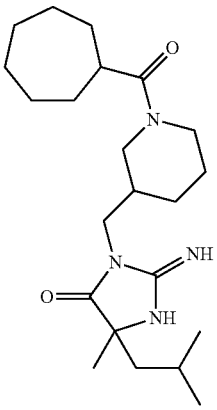
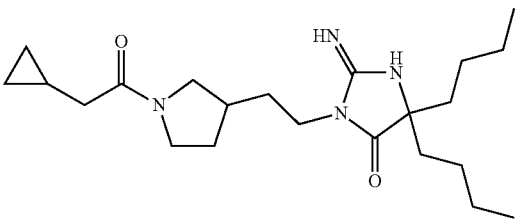
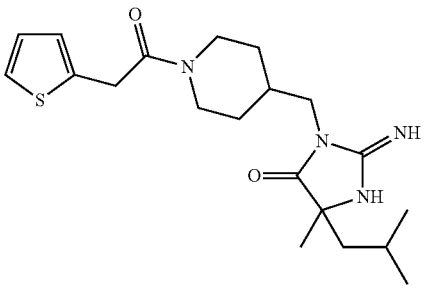
#	Structure	MW	Obs. m/e
1008		390	391
1009		390	391
1010		390	391
1011		390	391

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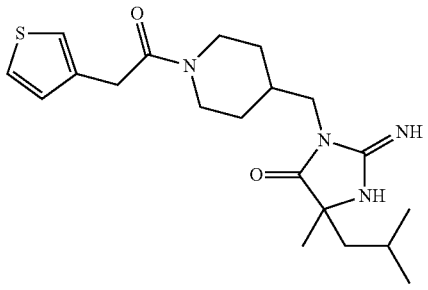
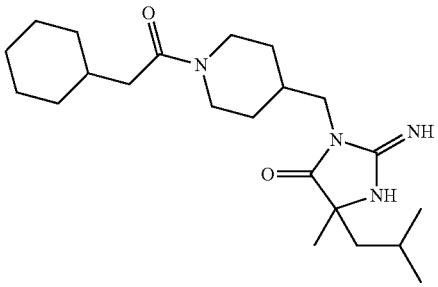
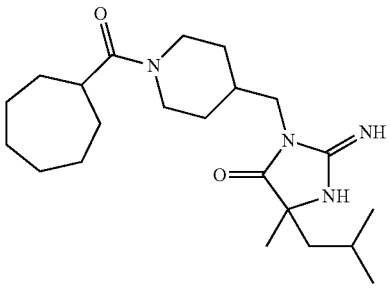
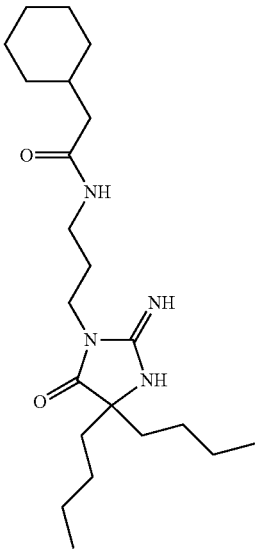
#	Structure	MW	Obs. m/e
1012		390	391
1013		390	391
1014		390	391
1015		392	393

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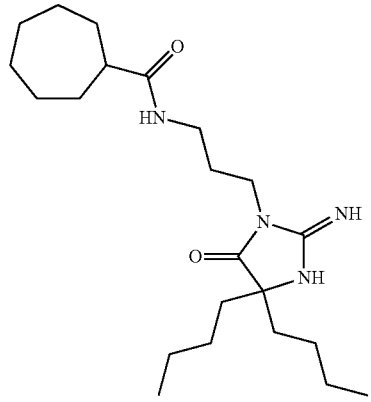
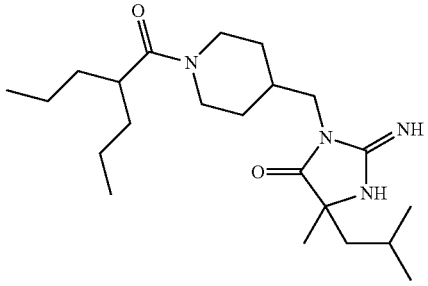
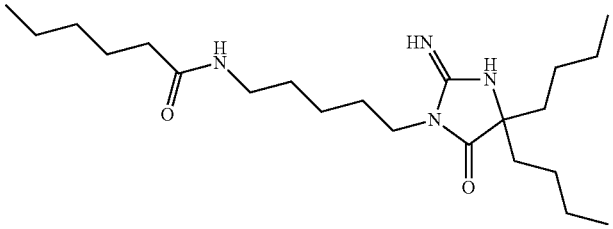
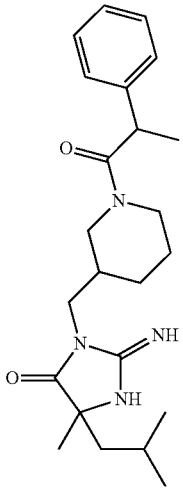
#	Structure	MW	Obs. m/e
1016		392	393
1017		392	393
1018		394	395
1019		398	399

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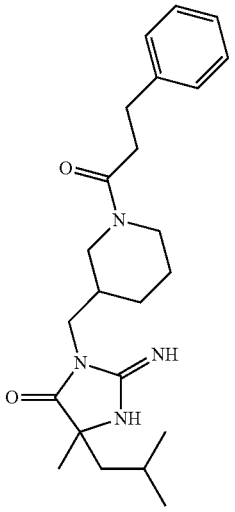
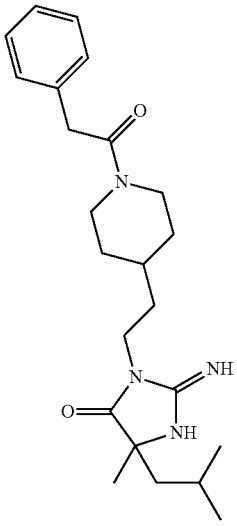
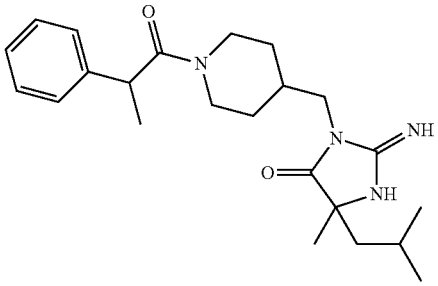
#	Structure	MW	Obs. m/e
1020		398	399
1021		398	399
1022		398	399

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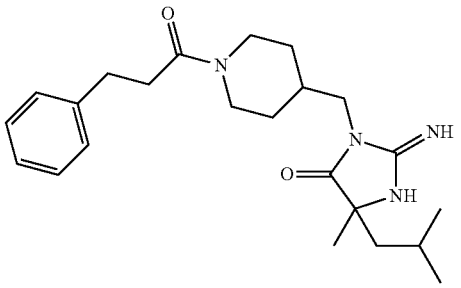
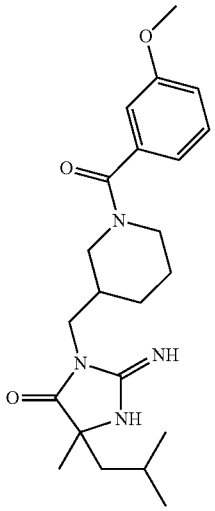
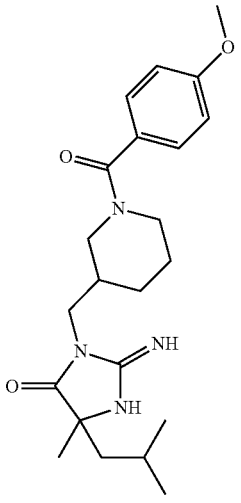
#	Structure	MW	Obs. m/e
1023		398	399
1024		400	401
1025		400	401

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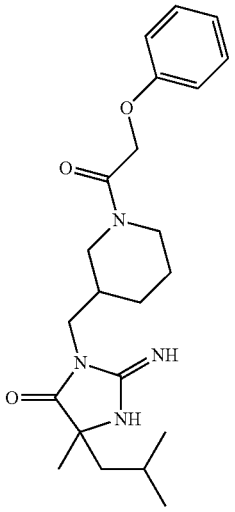
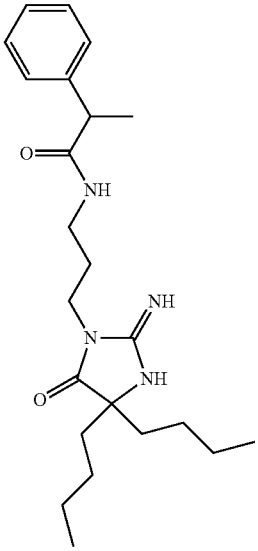
#	Structure	MW	Obs. m/e
1026		400	401
1027		400	401

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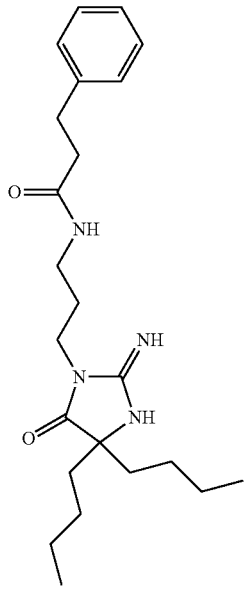
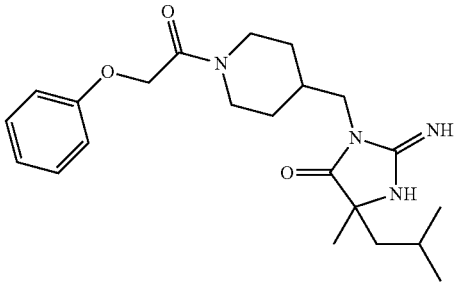
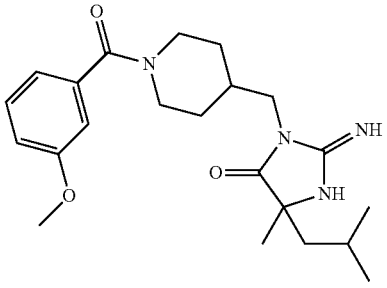
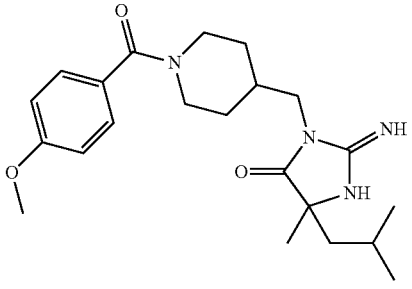
#	Structure	MW	Obs. m/e
1028		400	401
1029		400	401
1030		400	401
1031		400	401

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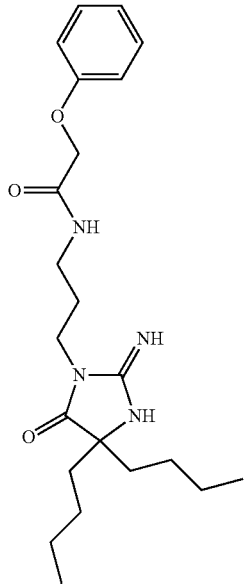
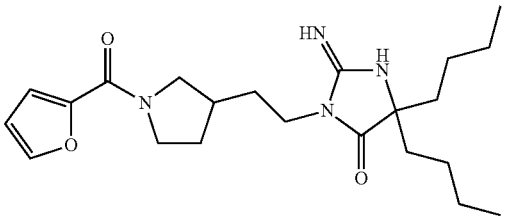
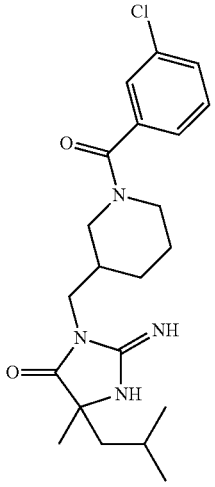
#	Structure	MW	Obs. m/e
1032		102	403
1033		402	403
1034		404	405

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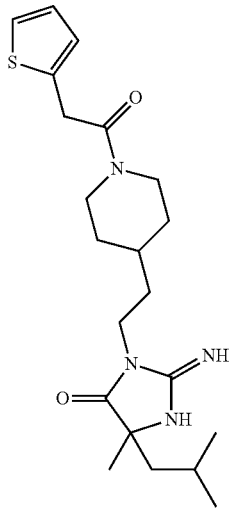
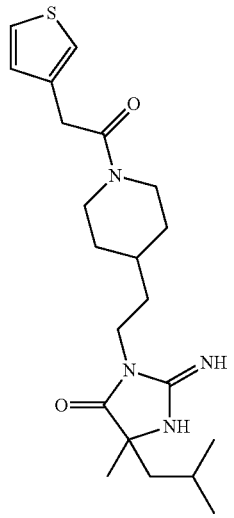
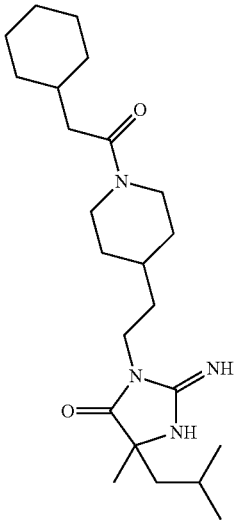
#	Structure	MW	Obs. m/e
1035		404	405
1036		404	405
1037		404	405

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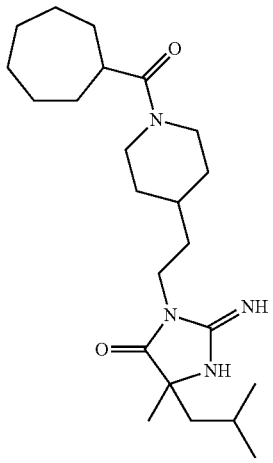
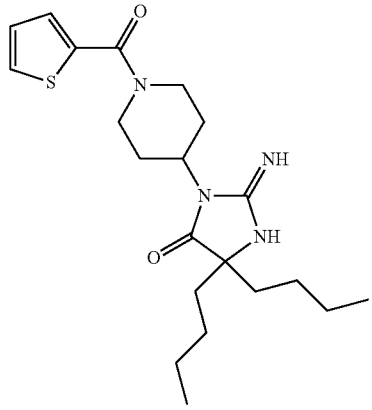
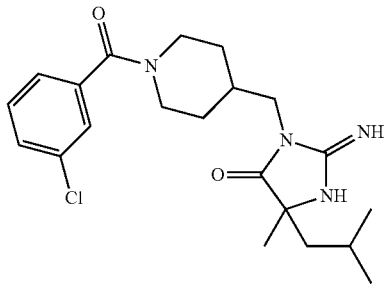
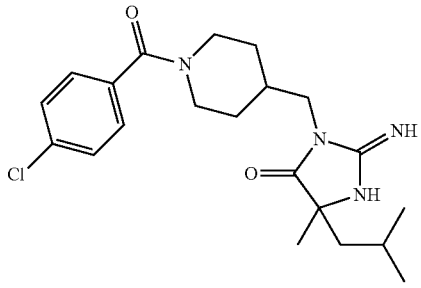
#	Structure	MW	Obs. m/e
1038		404	405
1039		404	405
1040		404	405
1041		404	405

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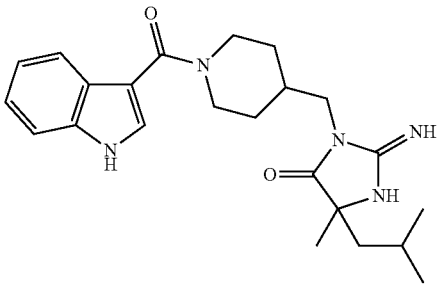
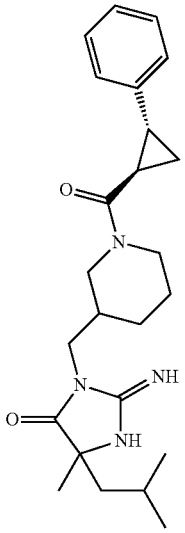
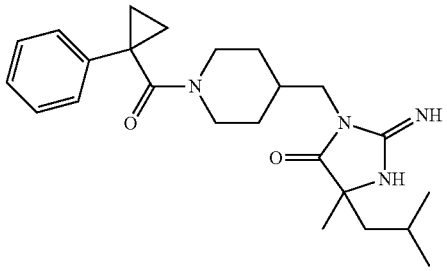
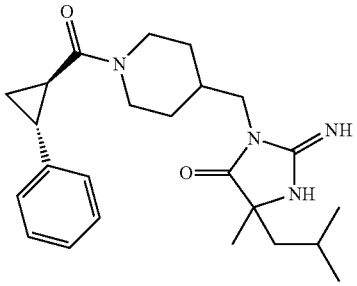
#	Structure	MW	Obs. m/e
1042		409	410
1043		410	411
1044		0	411
1045		410	411

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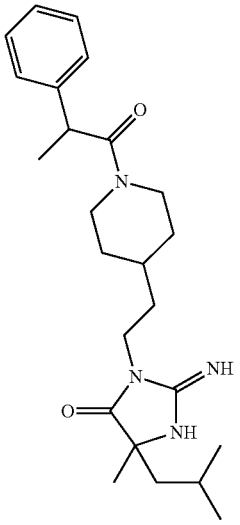
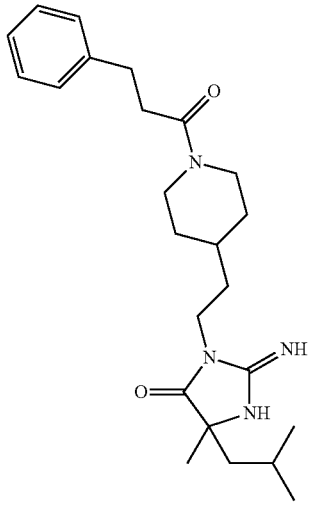
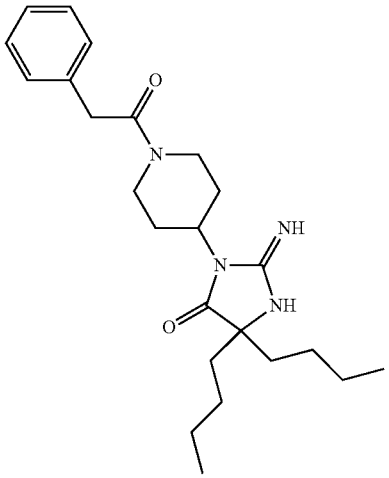
#	Structure	MW	Obs. m/e
1046		412	413
1047		412	413
1048		412	413

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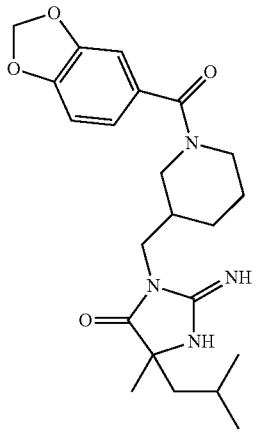
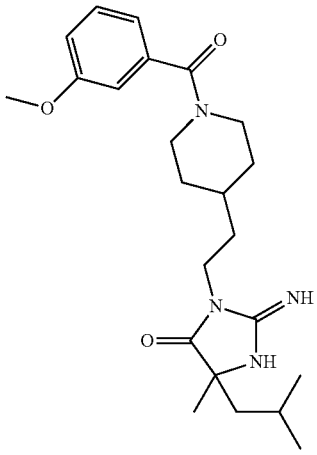
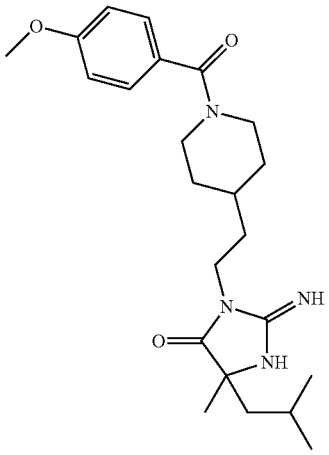
#	Structure	MW	Obs. m/e
1049		414	415
1050		414	415
1051		414	415

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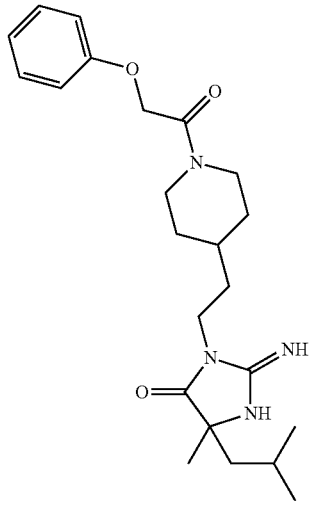
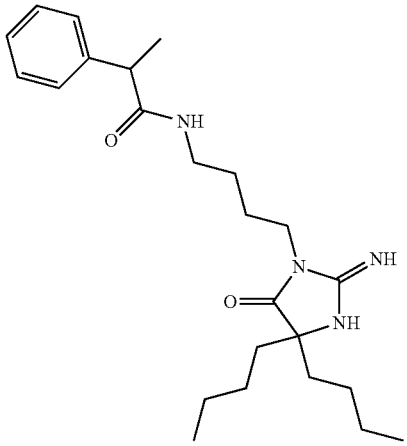
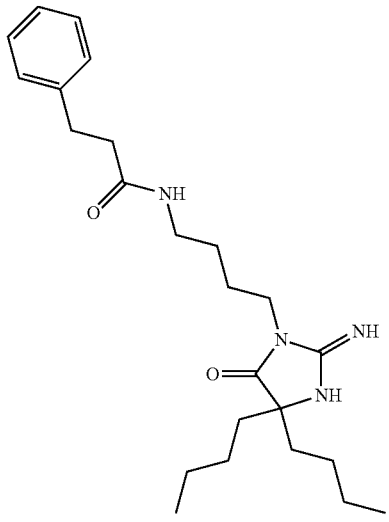
#	Structure	MW	Obs. m/e
1052		414	415
1053		414	415
1054		414	415

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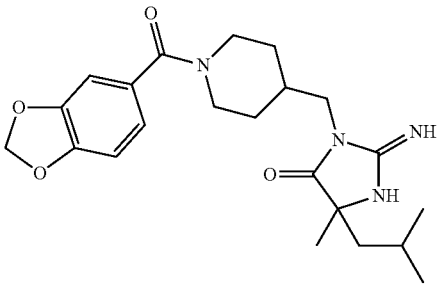
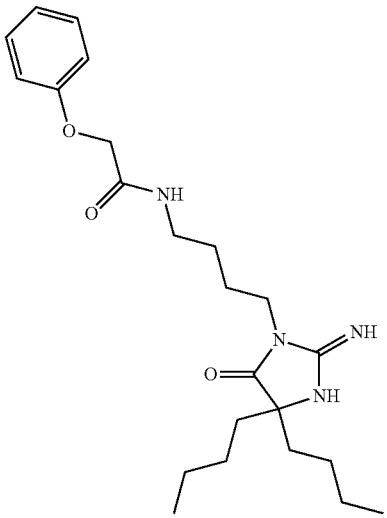
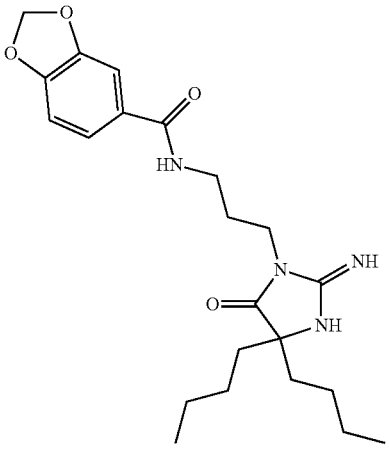
#	Structure	MW	Obs. m/e
1055		414	415
1056		416	417
1057		416	417

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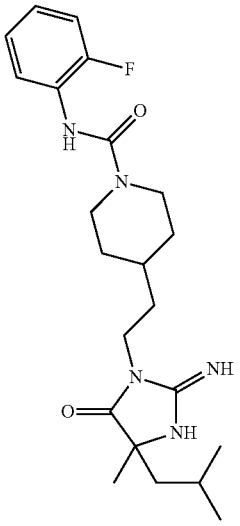
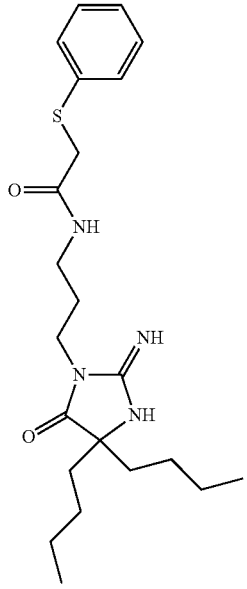
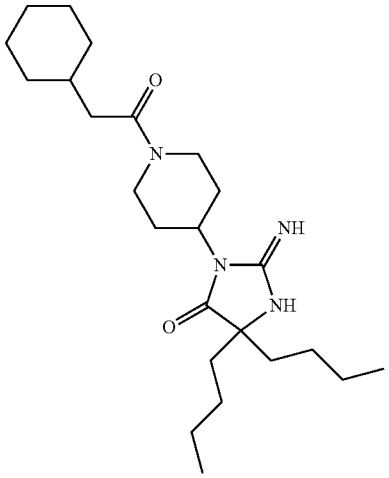
#	Structure	MW	Obs. m/e
1058		417	418
1059		418	419
1060		418	419

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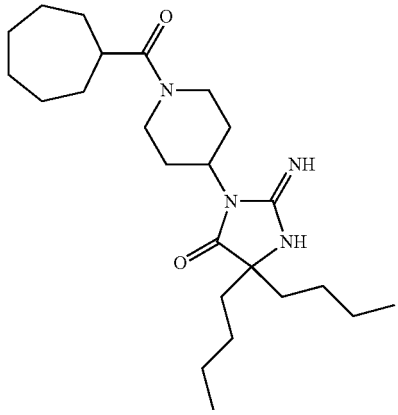
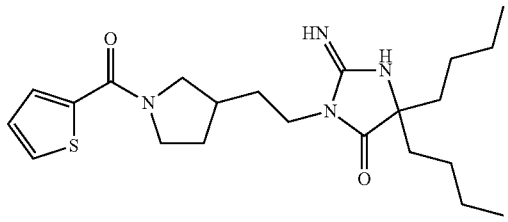
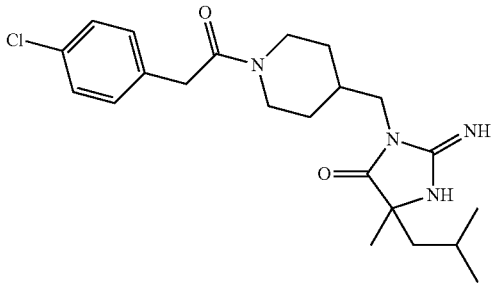
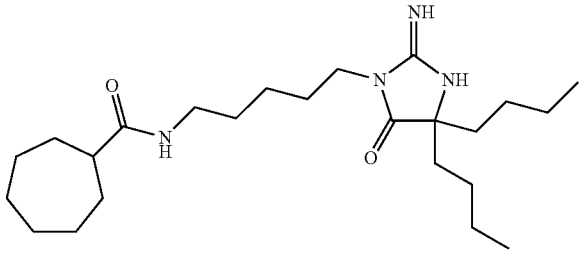
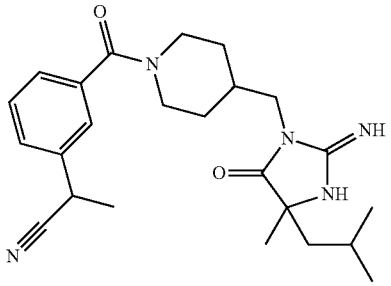
#	Structure	MW	Obs. m/e
1061		418	419
1062		418	419
1063		418	419
1064		420	421
1065		423	424

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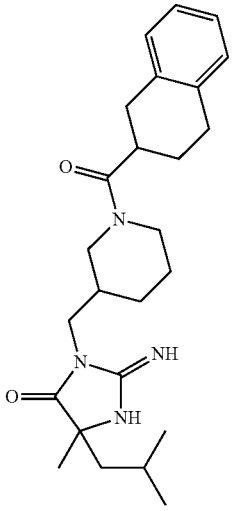
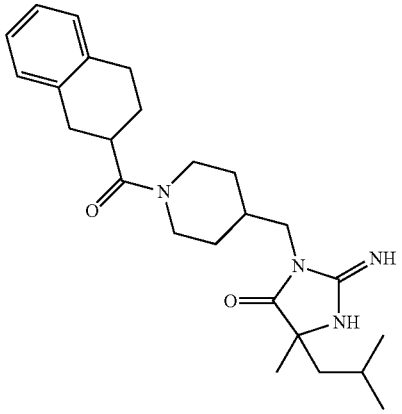
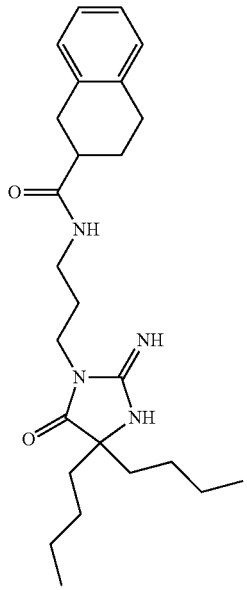
#	Structure	MW	Obs. m/e
1066		424	425
1067		424	425
1068		426	427

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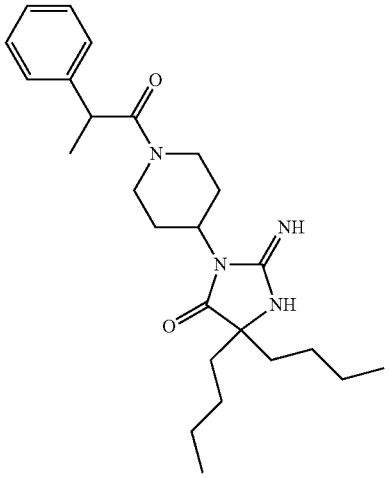
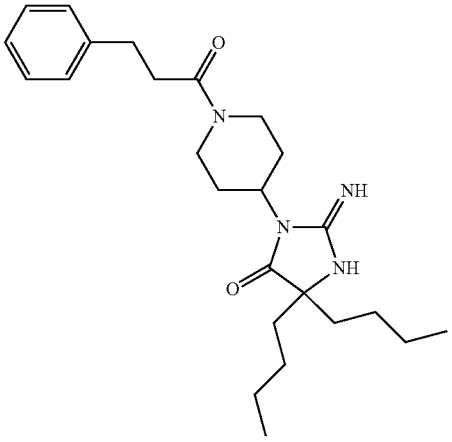
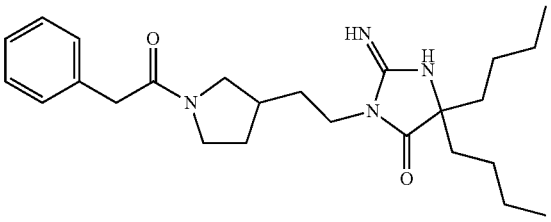
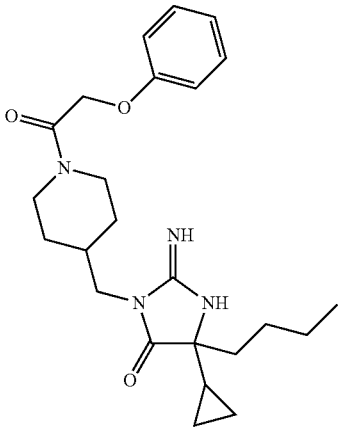
#	Structure	MW	Obs. m/e
1069		426	427
1070		426	427
1071		426	427
1072		426	427

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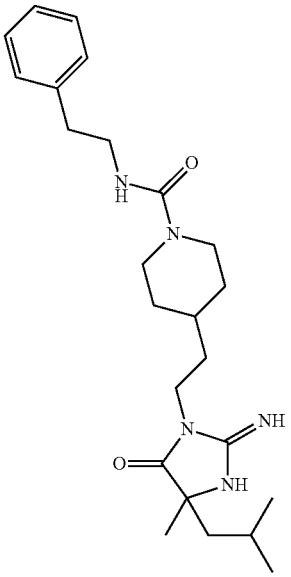
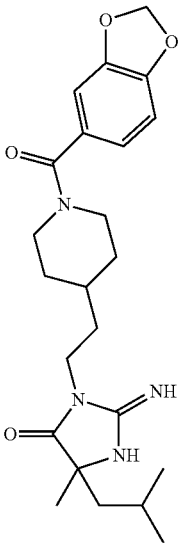
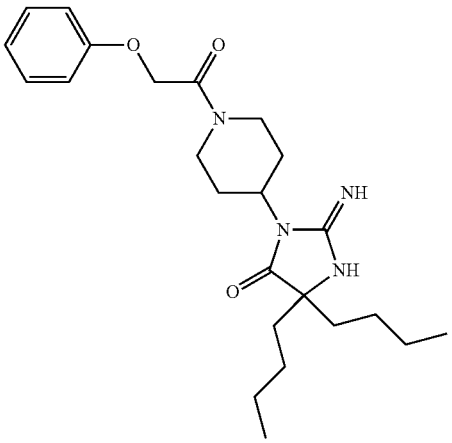
#	Structure	MW	Obs. m/e
1073		427	428
1074		428	429
1075		428	429

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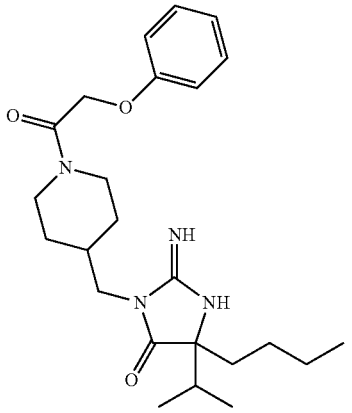
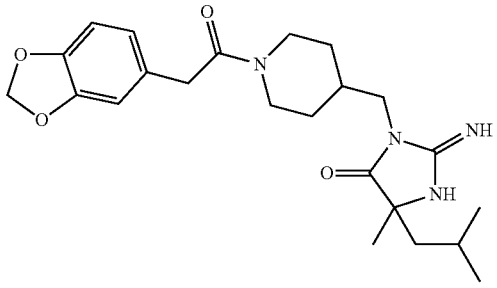
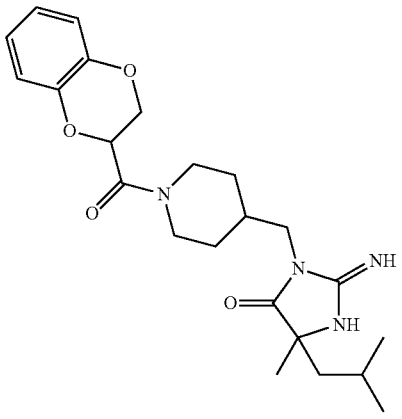
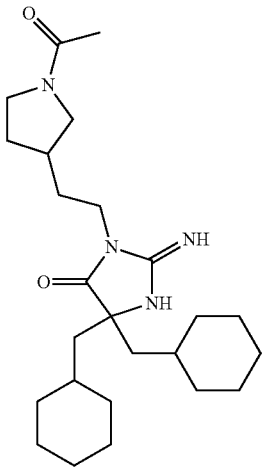
#	Structure	MW	Obs. m/e
1076		428	429
1077		428	429
1078		428	429
1079		430	431

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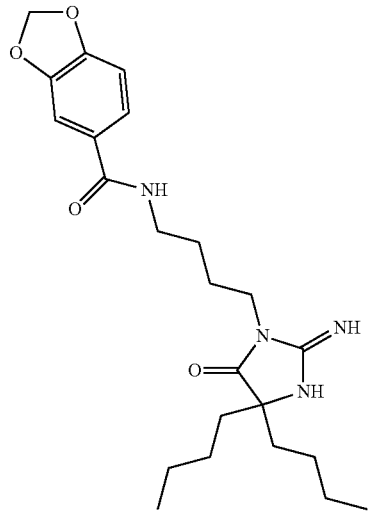
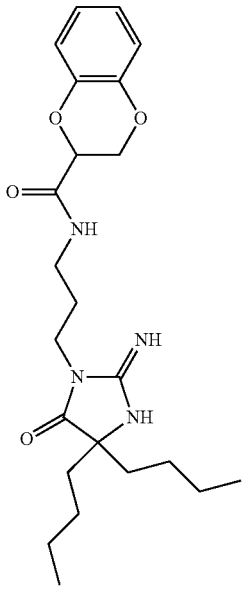
#	Structure	MW	Obs. m/e
1080		430	431
1081		430	431

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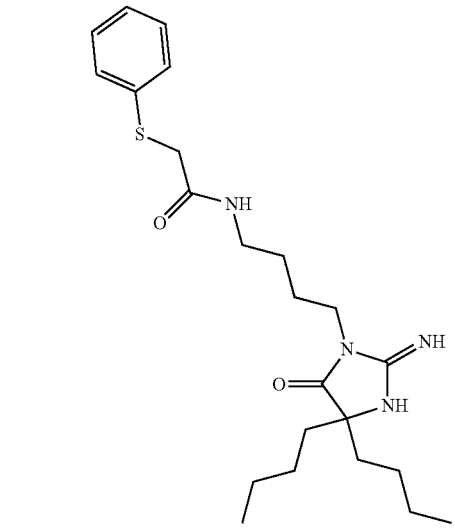
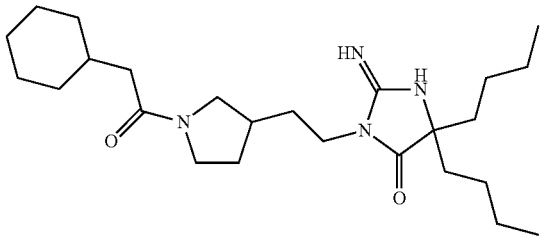
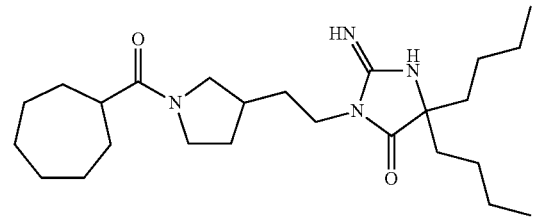
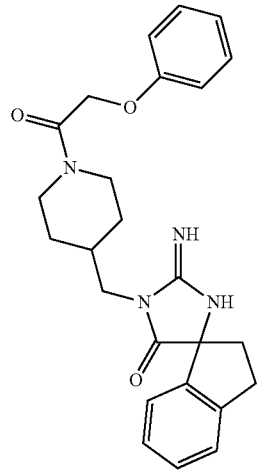
#	Structure	MW	Obs. m/e
1082		432	433
1083		432	433
1084		432	433
1085		432	433

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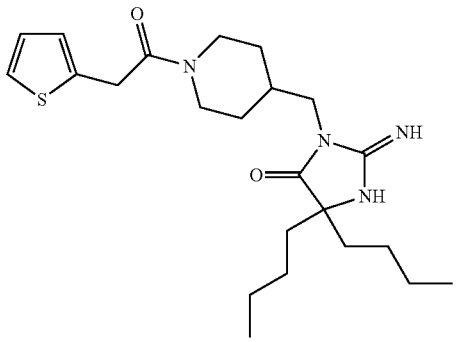
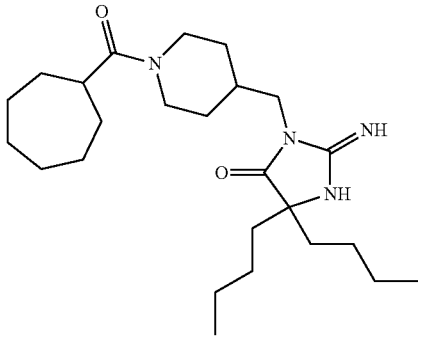
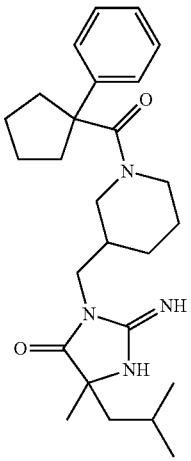
#	Structure	MW	Obs. m/e
1086		432	433
1087		432	433
1088		438	439

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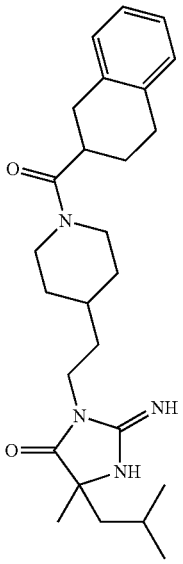
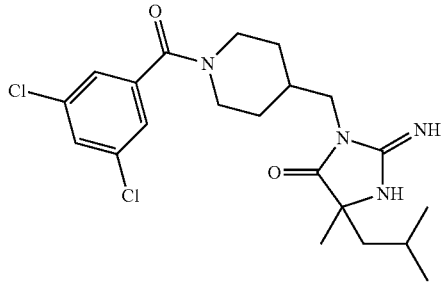
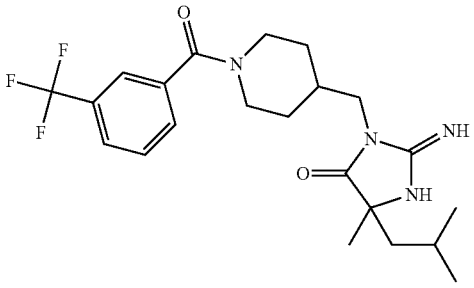
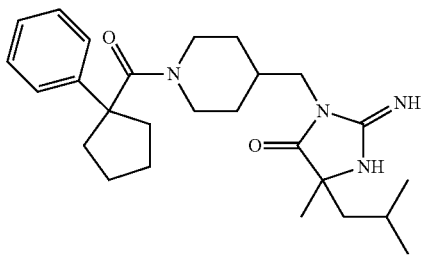
#	Structure	MW	Obs. m/e
1089		438	439
1090		438	439
1091		438	439
1092		438	439

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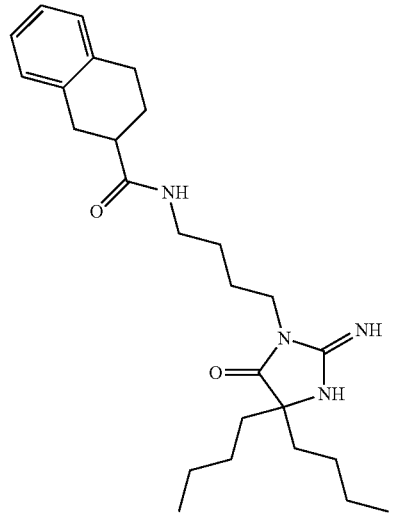
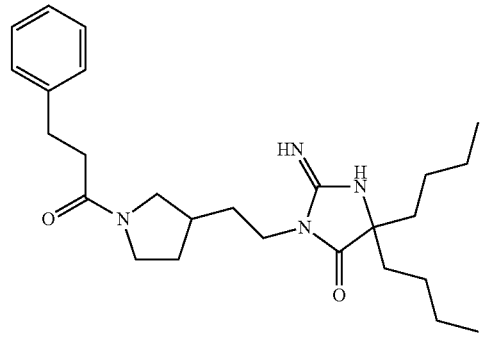
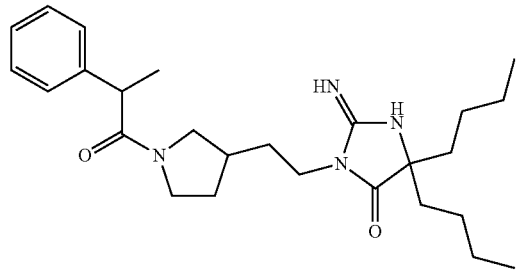
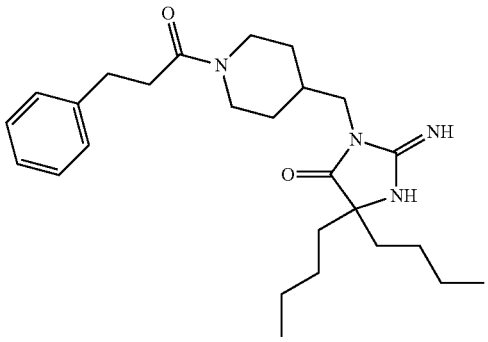
#	Structure	MW	Obs. m/e
1093		440	441
1094		440	441
1095		440	441
1096		440	441

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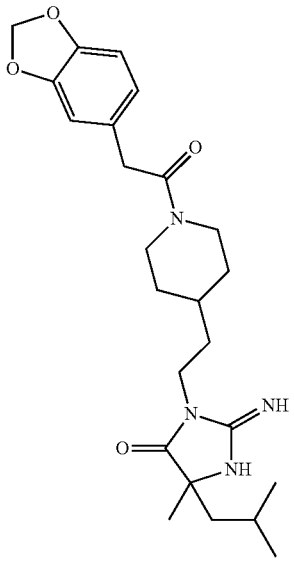
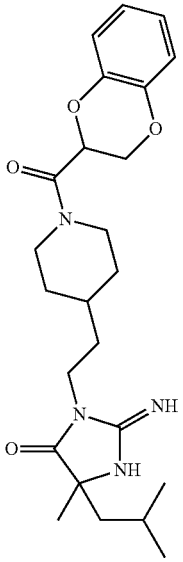
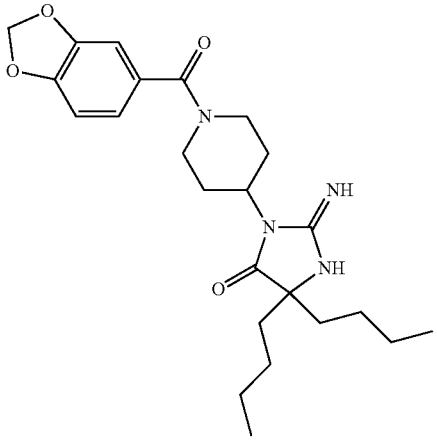
#	Structure	MW	Obs. m/e
1097		442	443
1098		442	443
1099		442	443

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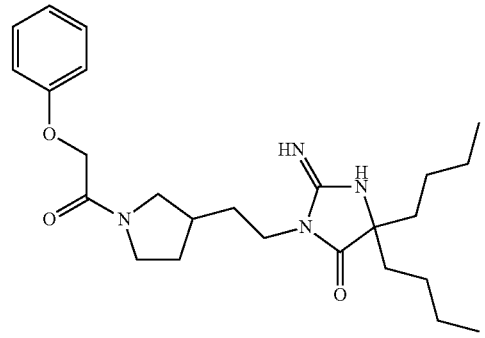
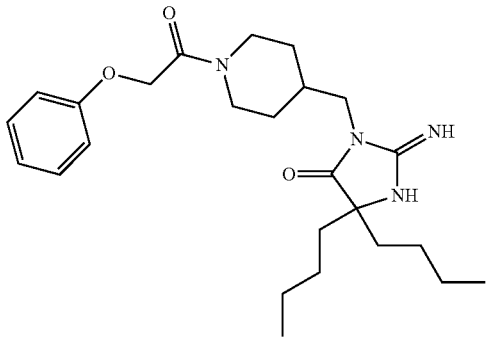
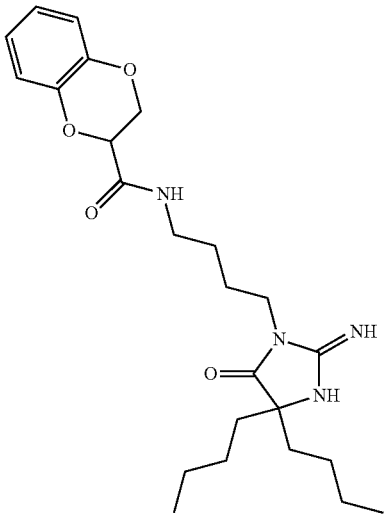
#	Structure	MW	Obs. m/e
1100		442	443
1101		442	443
1102		444	445

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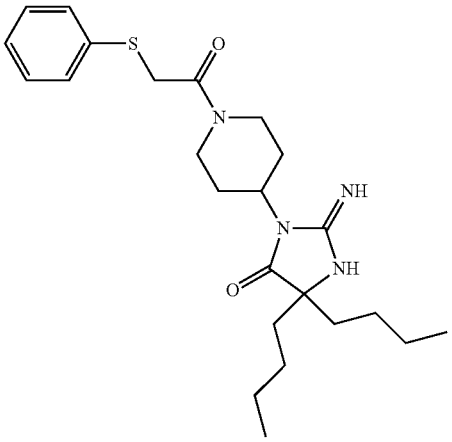
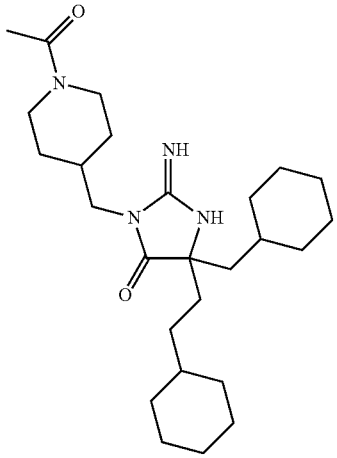
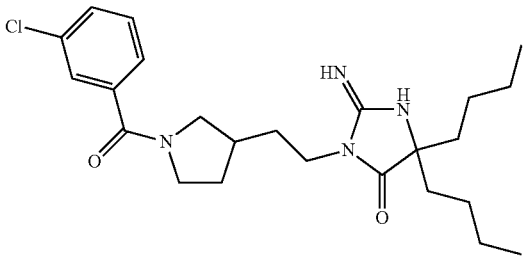
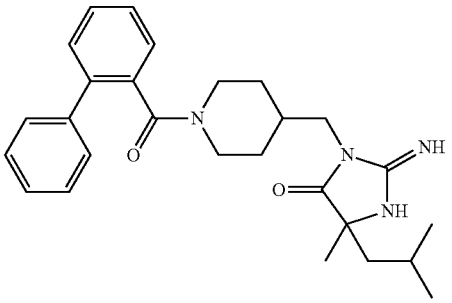
#	Structure	MW	Obs. m/e
1103		444	445
1104		444	445
1105		446	447
1106		446	447

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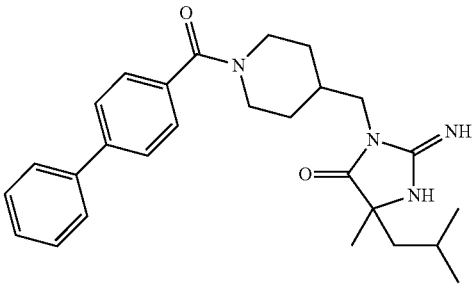
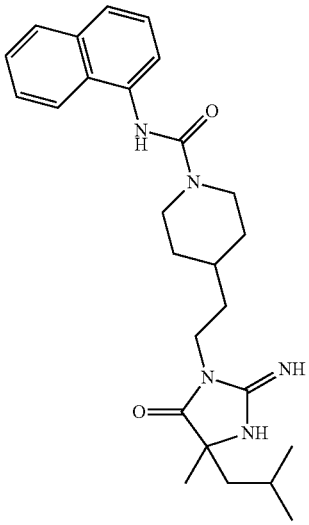
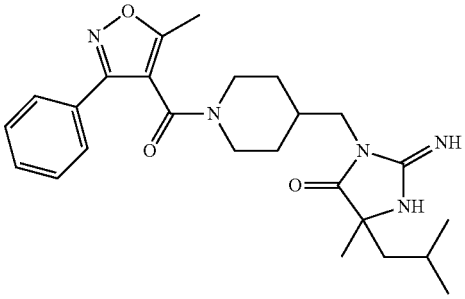
#	Structure	MW	Obs. m/e
1107		446	447
1108		449	450
1109		451	452

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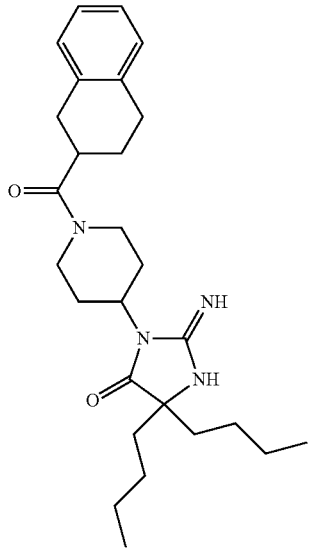
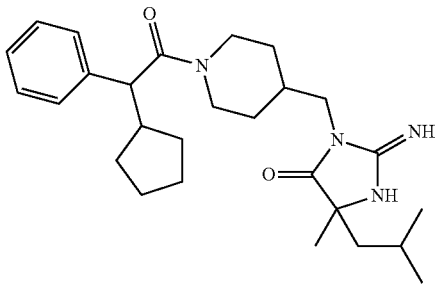
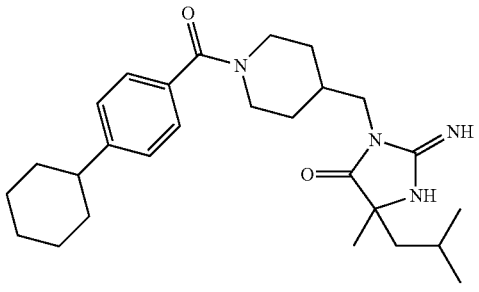
#	Structure	MW	Obs. m/e
1110		452	453
1111		452	453
1112		452	453

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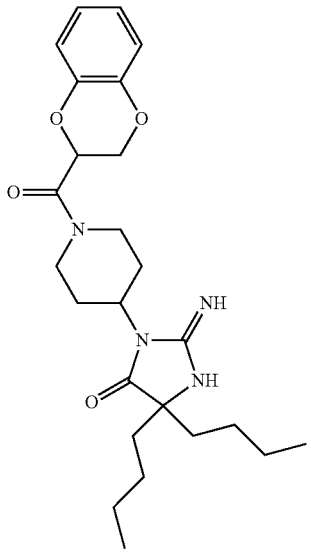
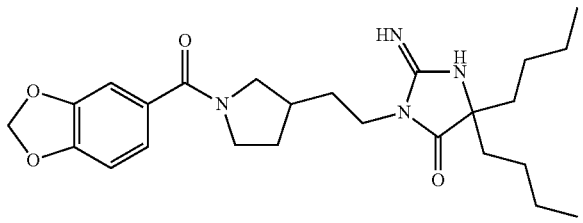
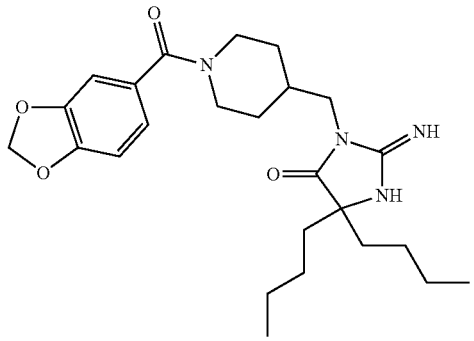
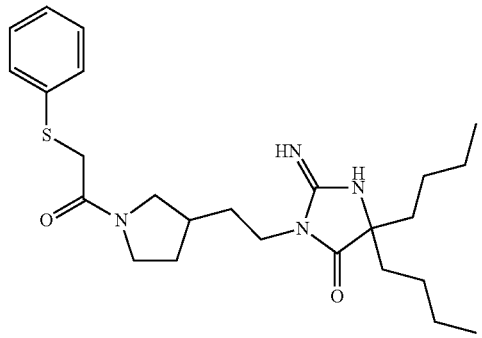
#	Structure	MW	Obs. m/e
1113		456	457
1114		456	457
1115		456	457
1116		458	459

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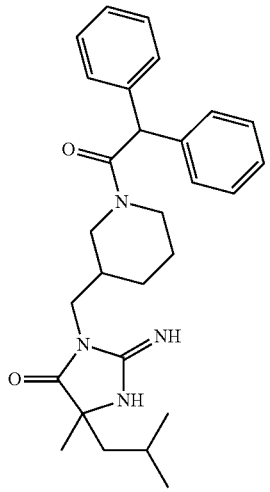
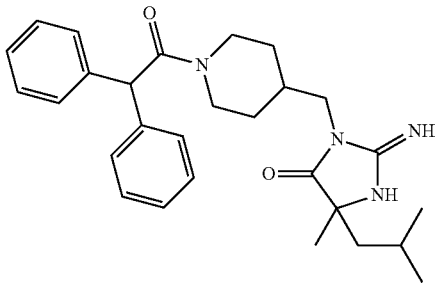
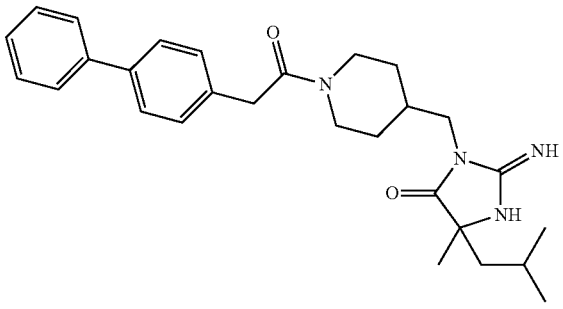
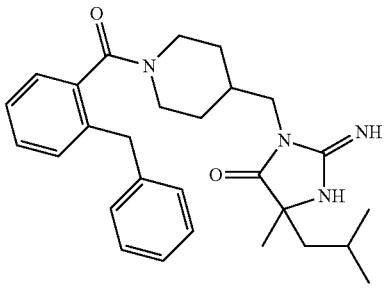
#	Structure	MW	Obs. m/e
1117		460	461
1118		460	461
1119		460	461
1120		460	461

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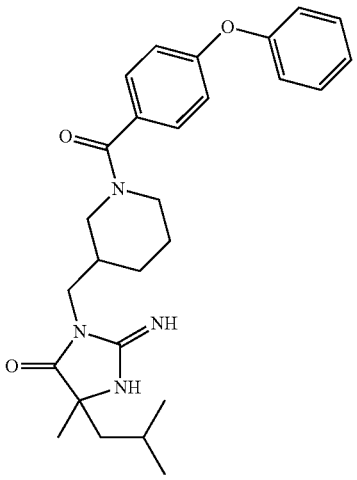
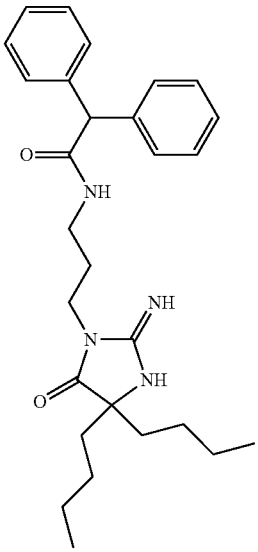
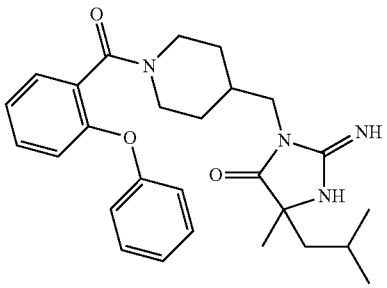
#	Structure	MW	Obs. m/e
1121		462	463
1122		462	463
1123		462	463

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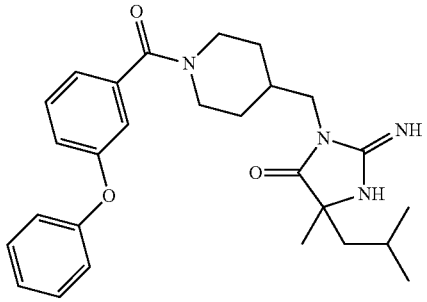
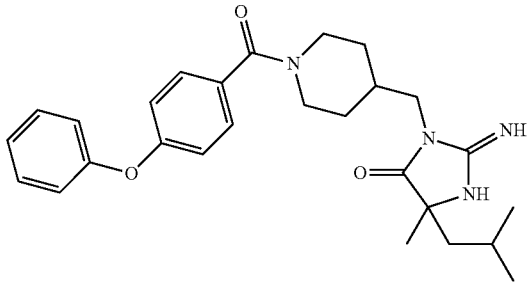
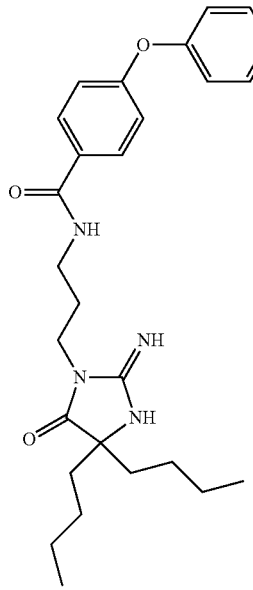
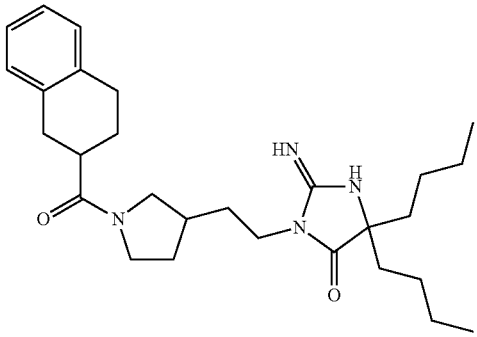
#	Structure	MW	Obs. m/e
1124		462	463
1125		462	463
1126		464	465
1127		466	467

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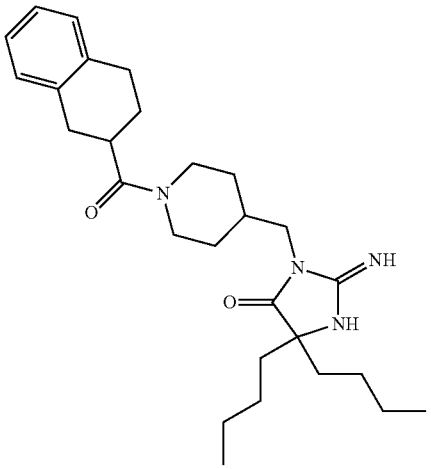
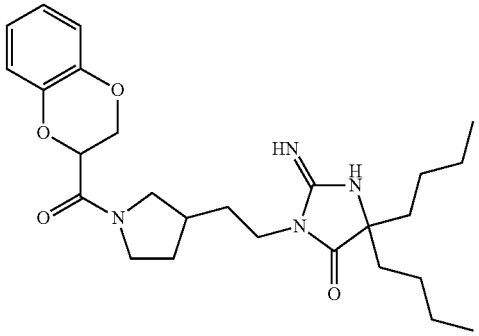
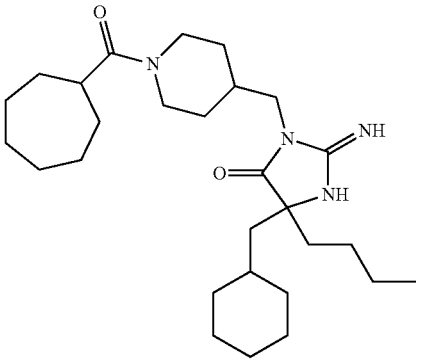
#	Structure	MW	Obs. m/e
1128		466	467
1129		470	471
1130		472	473

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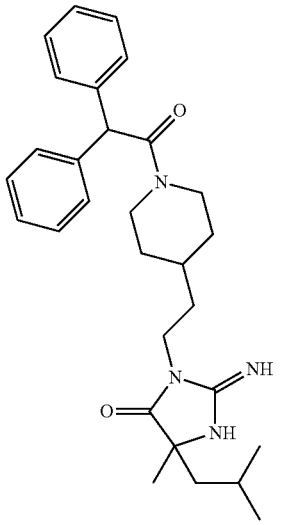
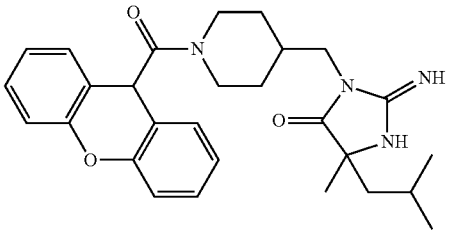
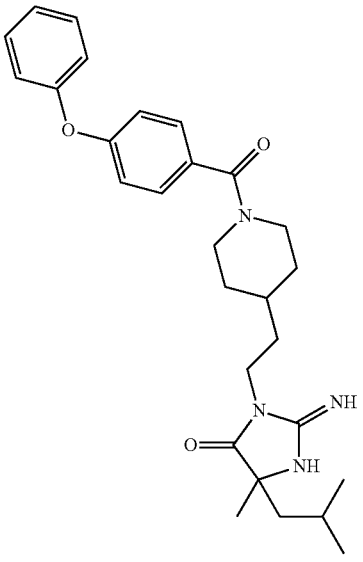
#	Structure	MW	Obs. m/e
1131		474	475
1132		474	475
1133		476	477

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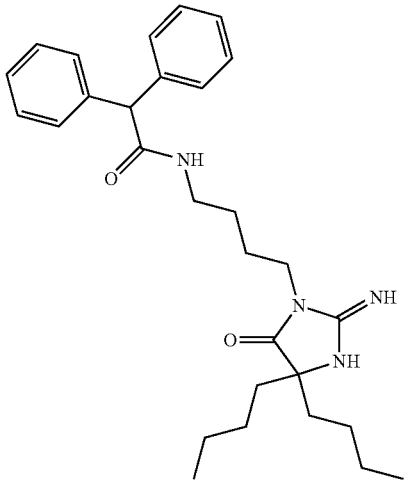
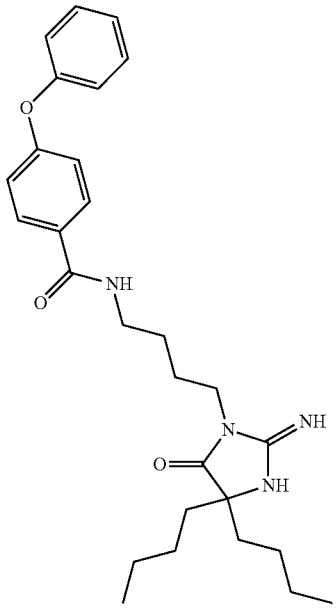
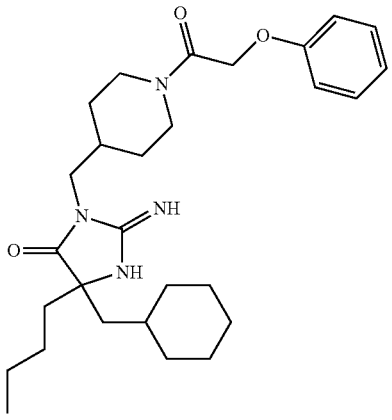
#	Structure	MW	Obs. m/e
1134		476	477
1135		478	479
1136		482	483

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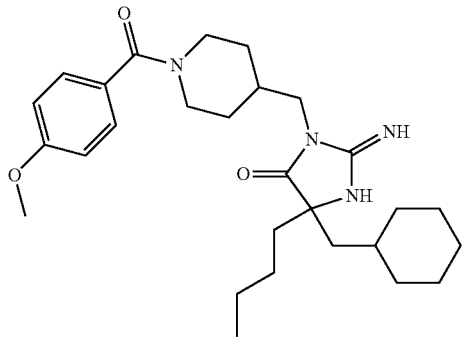
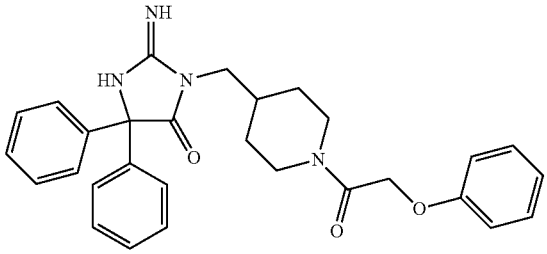
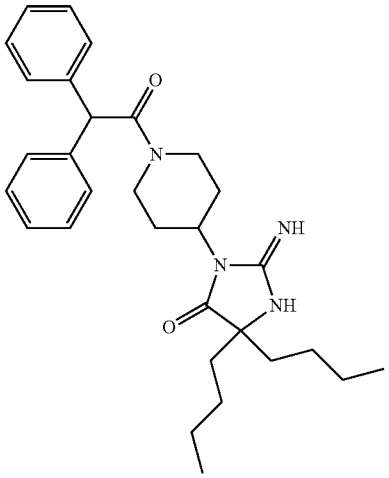
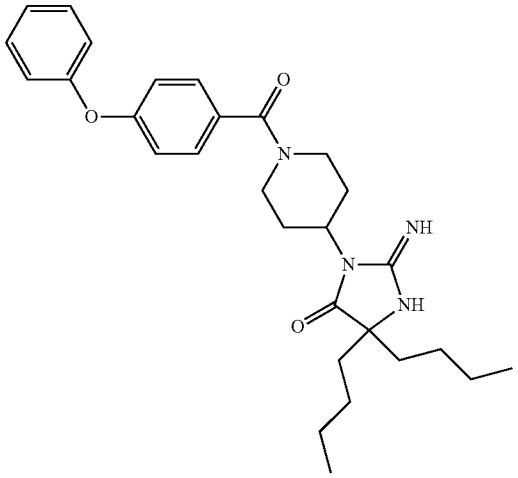
#	Structure	MW	Obs. m/e
1137		482	483
1138		482	483
1139		488	489
1140		490	491

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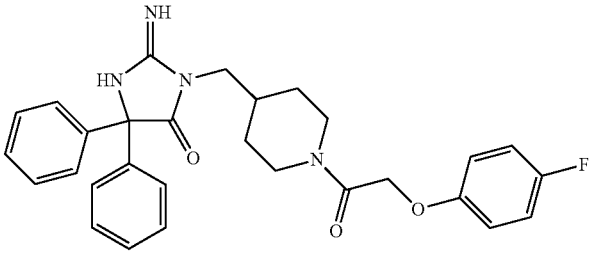
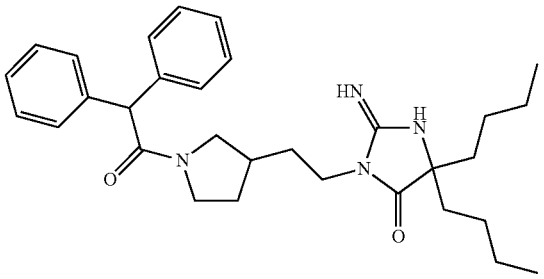
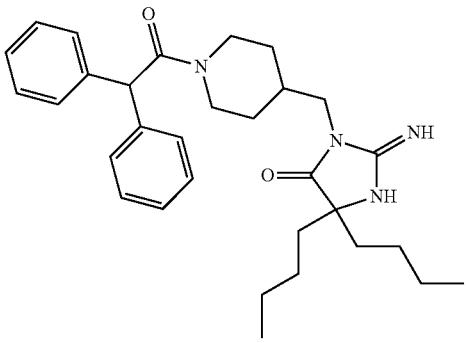
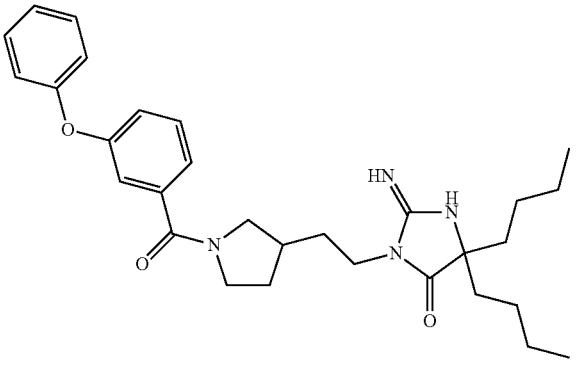
#	Structure	MW	Obs. m/e
1141		500	501
1142		502	503
1143		502	503
1144		504	505

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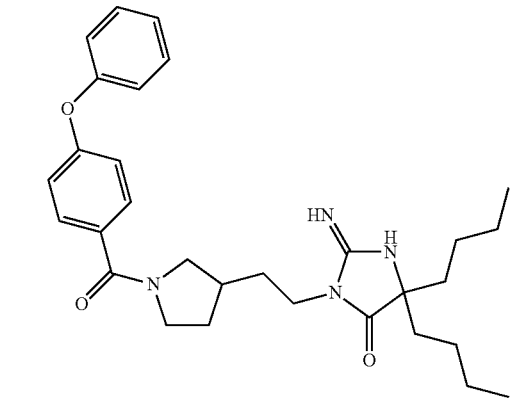
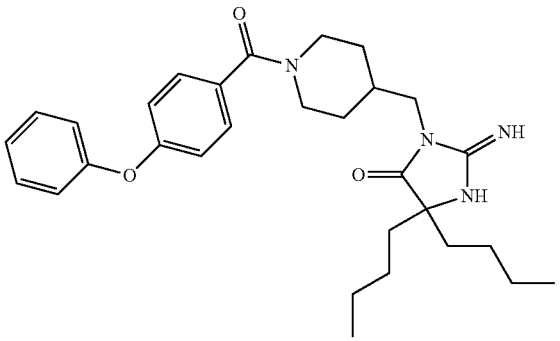
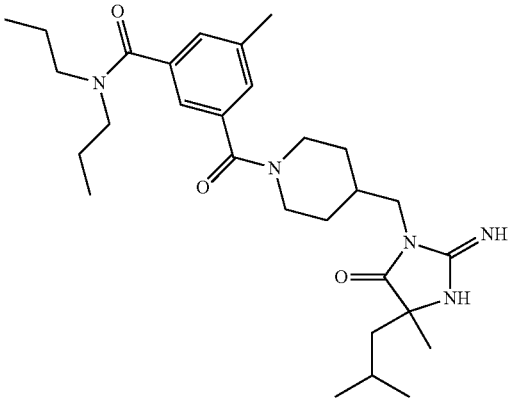
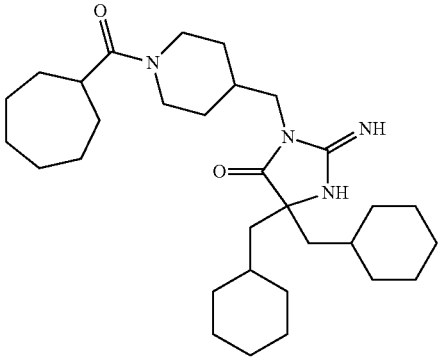
#	Structure	MW	Obs. m/e
1145		504	505
1146		504	505
1147		511	512
1148		512	513

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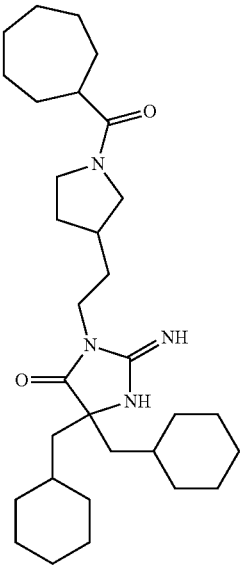
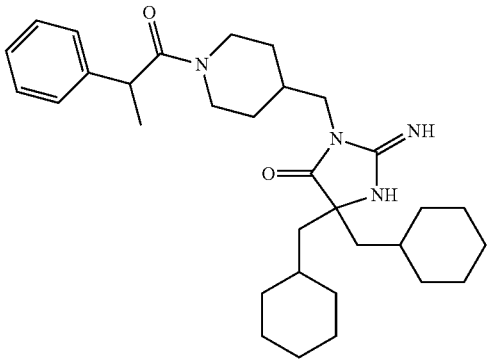
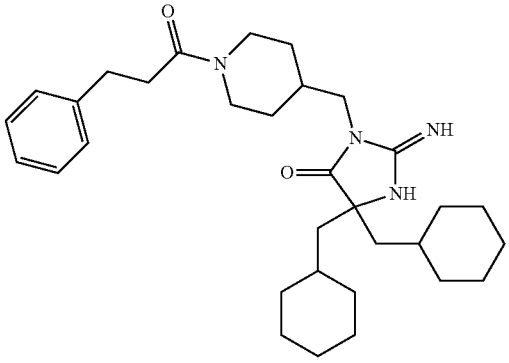
#	Structure	MW	Obs. m/e
1149		512	513
1150		520	521
1151		520	521

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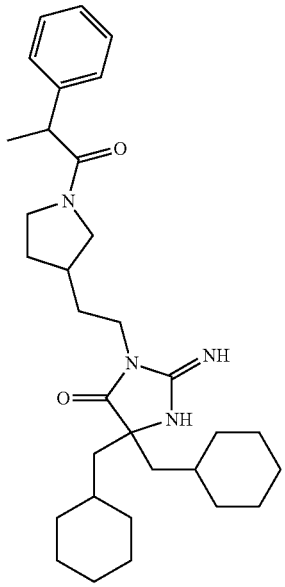
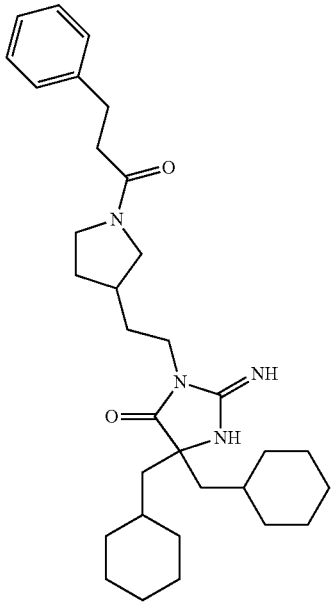
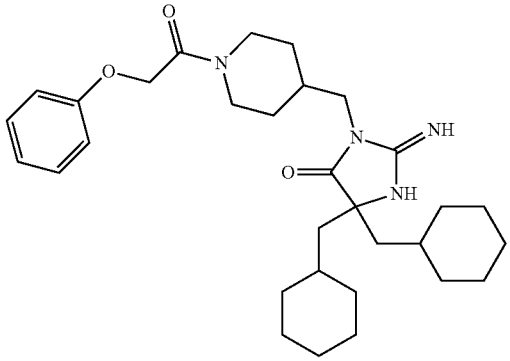
#	Structure	MW	Obs. m/e
1152		520	521
1153		520	521
1154		522	523

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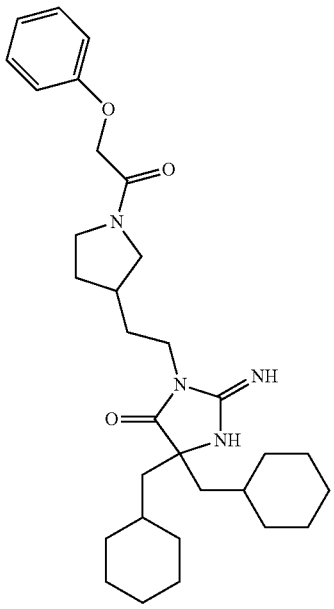
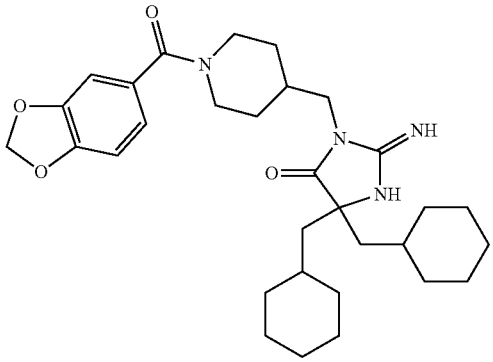
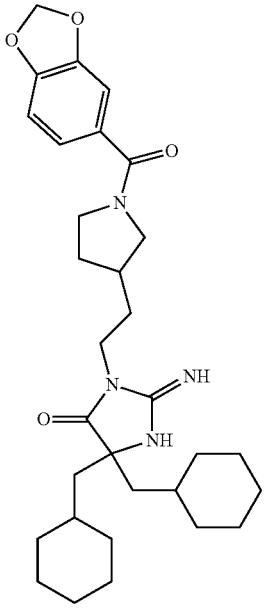
#	Structure	MW	Obs. m/e
1155		522	523
1156		536	537
1157		536	537

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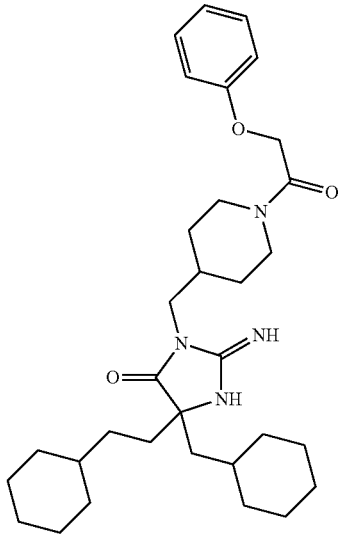
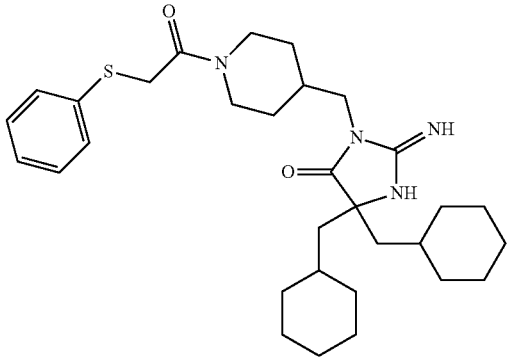
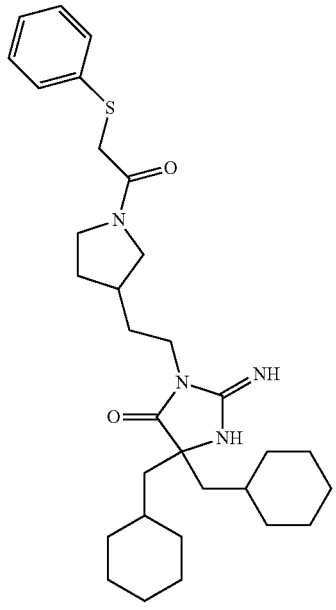
#	Structure	MW	Obs. m/e
1158		536	537
1159		538	539
1160		538	539

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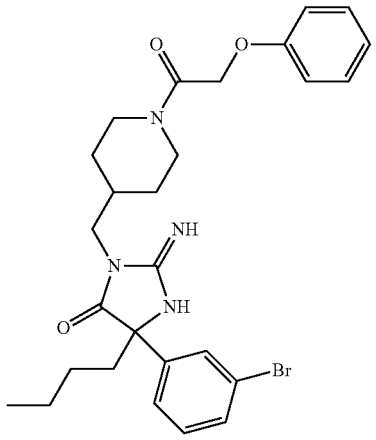
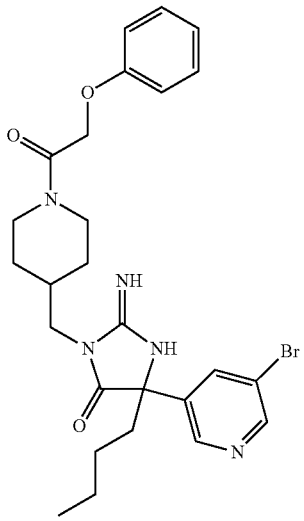
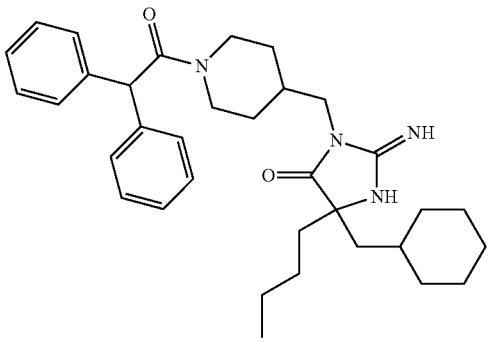
#	Structure	MW	Obs. m/e
1161		540	541
1162		541	542
1163		542	543

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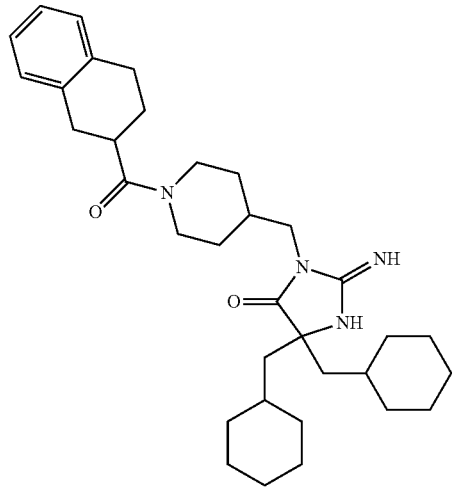
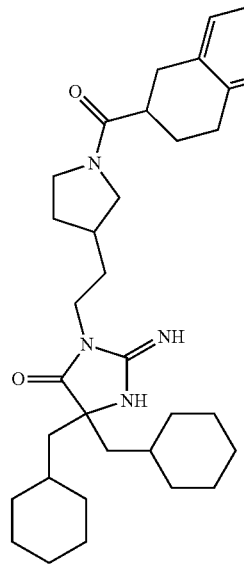
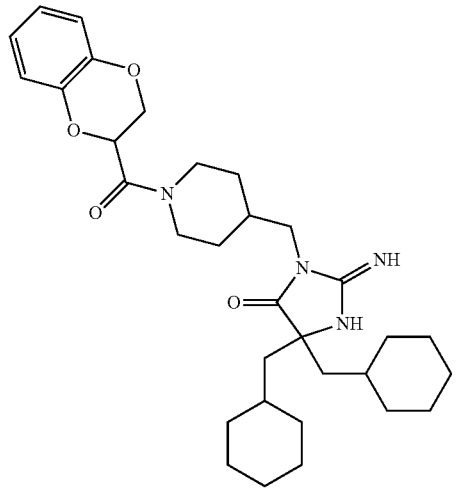
#	Structure	MW	Obs. m/e
1164		546	547
1165		546	547
1166		550	551

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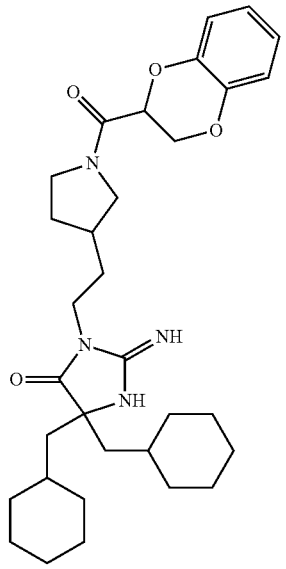
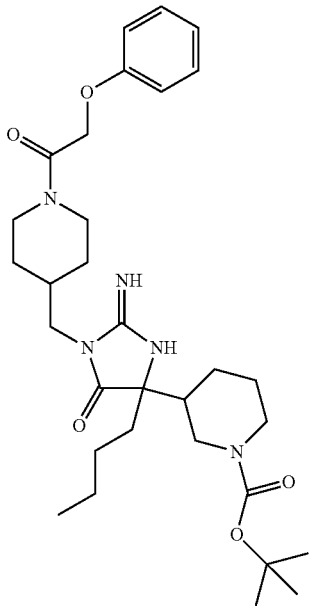
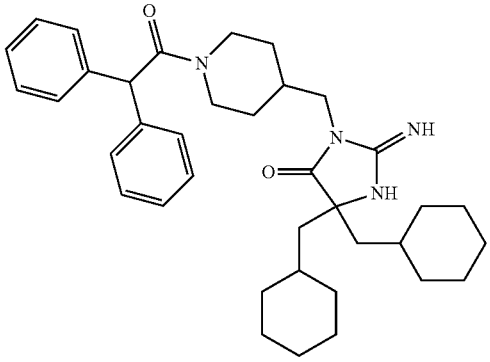
#	Structure	MW	Obs. m/e
1167		550	551
1168		569	570
1169		582	583

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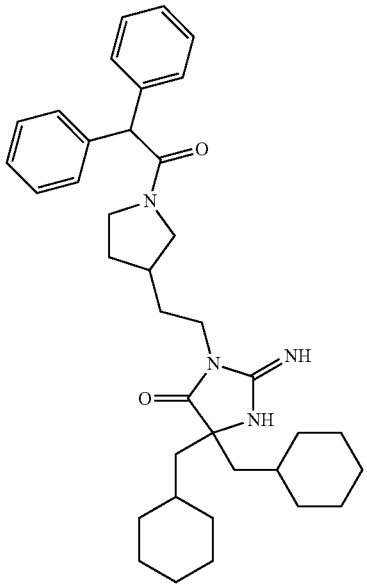
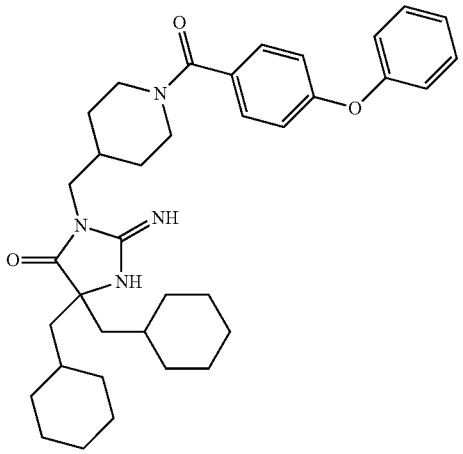
#	Structure	MW	Obs. m/e
1170		582	583
1171		584	585

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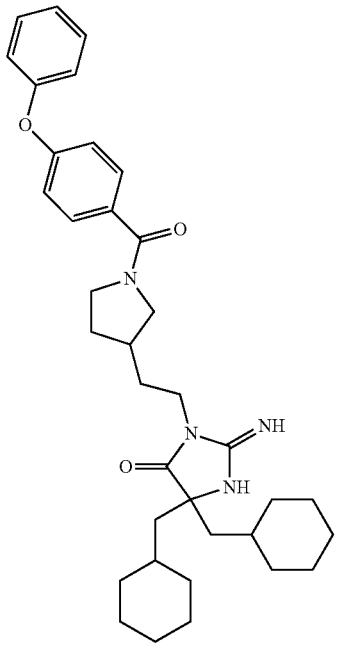
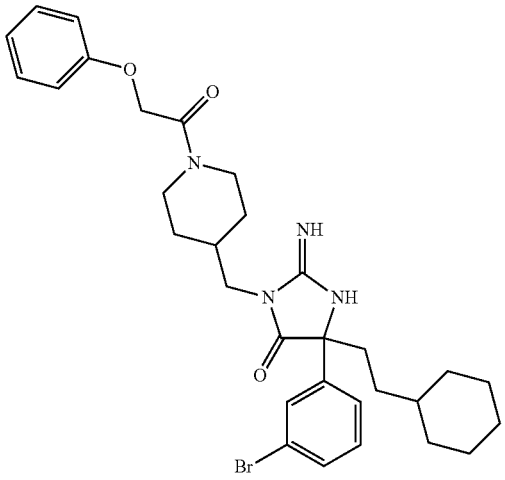
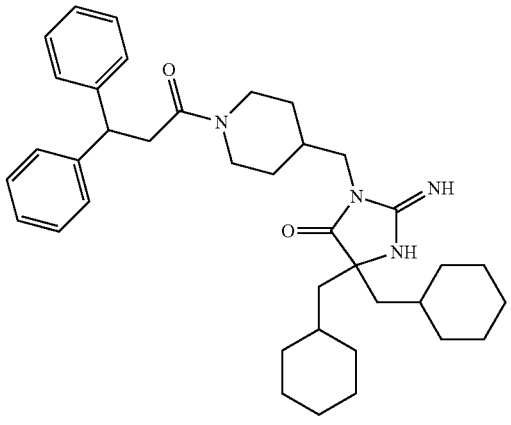
#	Structure	MW	Obs. m/e
1172		584	585
1173		594	595
1174		596	597

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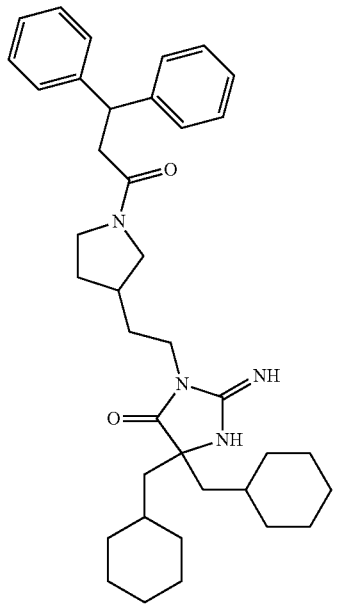
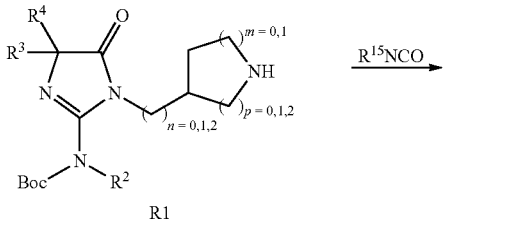
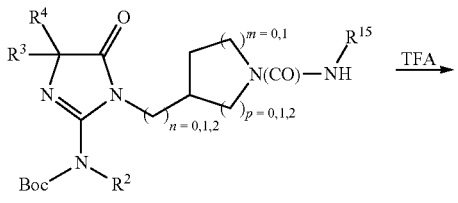
#	Structure	MW	Obs. m/e
1175		596	597

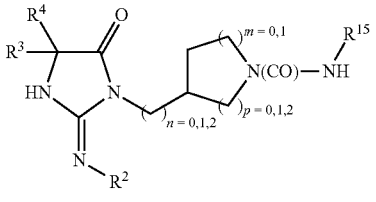
Method R



R1



R2



R3

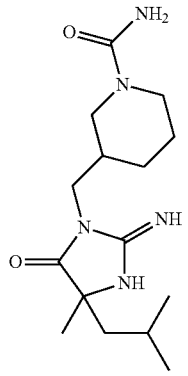
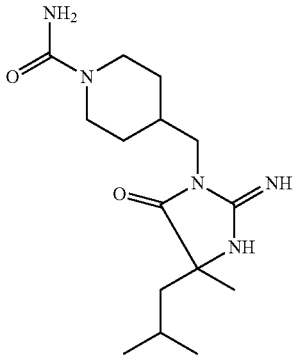
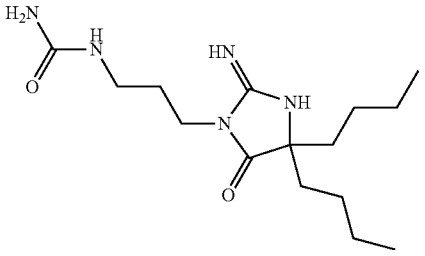
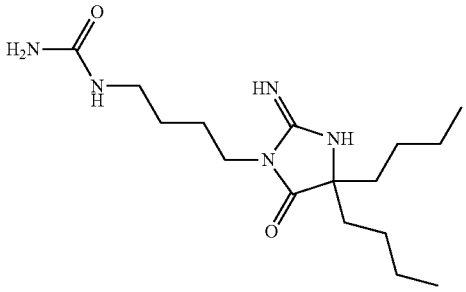
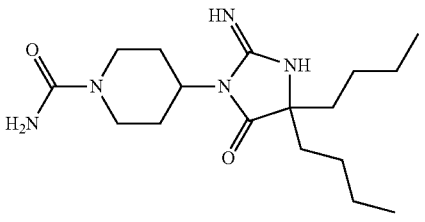
Method R, Step 1.

A solution of R^1 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu) (0.010 g) in acetonitrile (0.85 mL) and dichloroethane (0.15 mL) was put into a microtiter plate well followed by addition of 0.12 ml of 0.5M phenylisocyanate solution in dichloroethane. The well was sealed and the plate shaken for 20 h before the mixture was filtered and the solid washed with acetonitrile (0.5 ml). The combined solution was treated with Trisamine resin (0.050 g, 6 eq., 4.23 mmol/g) and Isocyanate resin (0.067 g, 3 eq., 1.53 mmol/g) and the mixture was shaken for 18 h. The mixture was filtered and the solution was evaporated to give the R2 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu and R^{15}=Ph).

Method R, Step 2.

Procedure similar to Method Q, step 6 was used for the transformation of R2 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu and R^{15}=Ph) to R3 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu and R^{15}=Ph).

The following compounds were prepared using similar methods:

#	Structure	MW	Obs. m/e
1176		309	310
1177		309	310
1178		311	312
1179		325	326
1180		337	338

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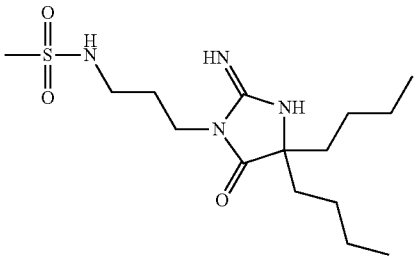
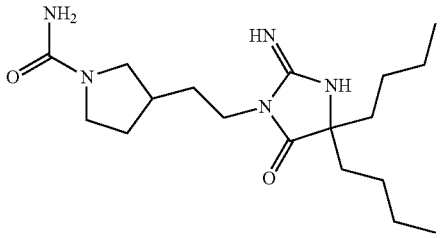
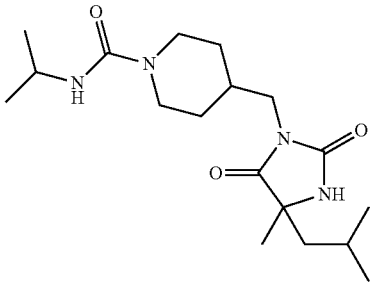
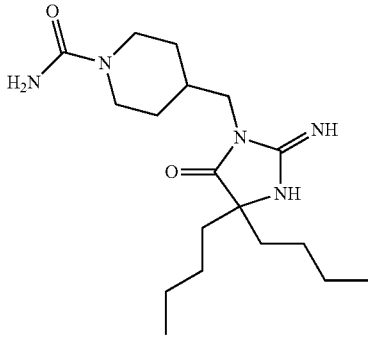
#	Structure	MW	Obs. m/e
1181		346	347
1182		351	352
1183		351	352
1184		351	352

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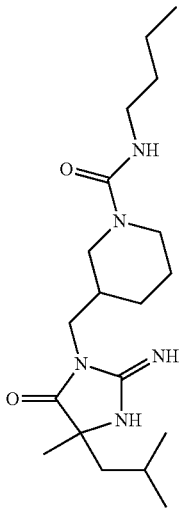
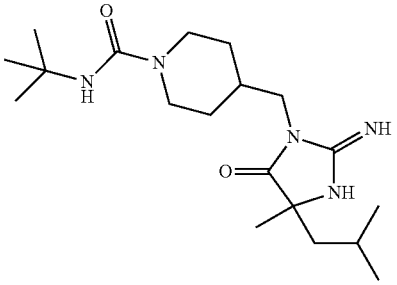
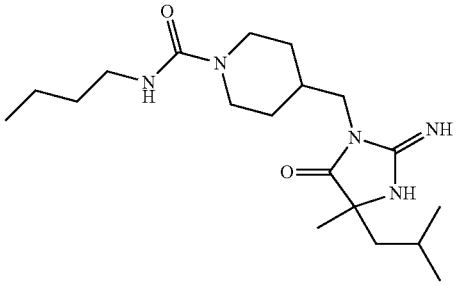
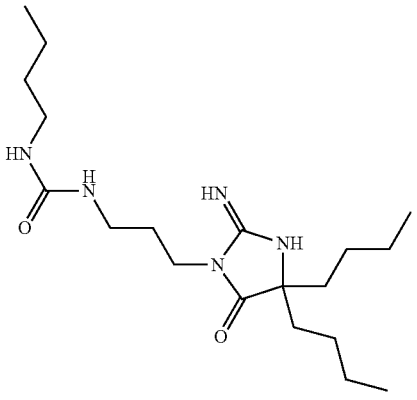
#	Structure	MW	Obs. m/e
1185		365	366
1186		365	366
1187		365	366
1188		367	368

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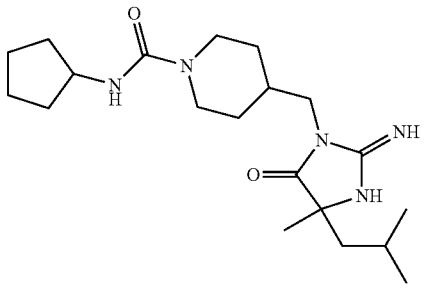
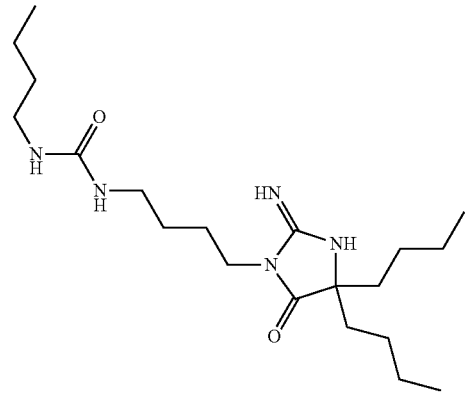
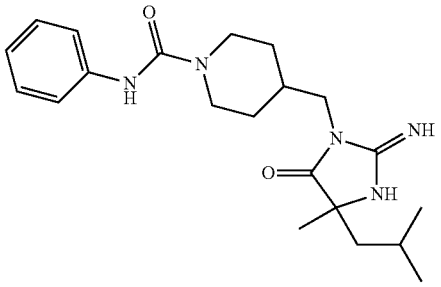
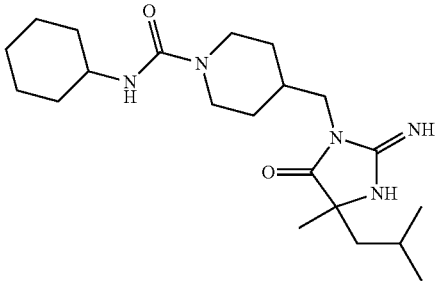
#	Structure	MW	Obs. m/e
1189		377	378
1190		381	382
1191		385	386
1192		391	392

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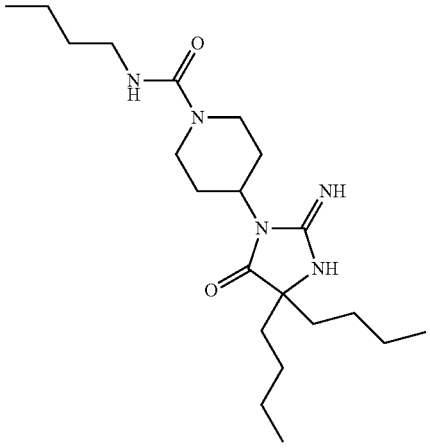
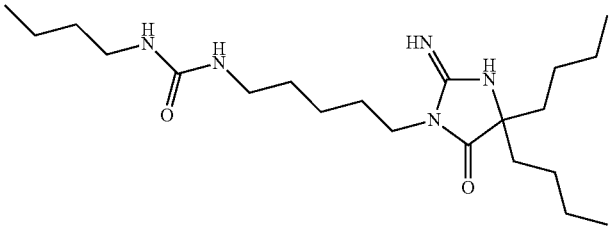
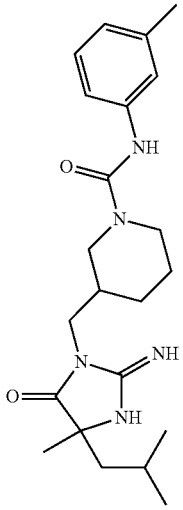
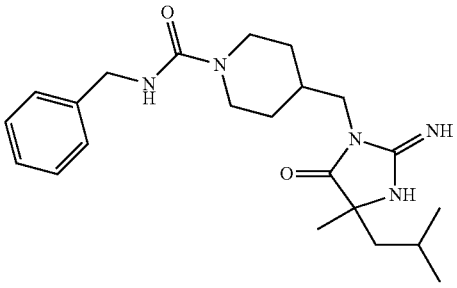
#	Structure	MW	Obs. m/e
1193		393	394
1194		395	396
1195		399	400
1196		399	400

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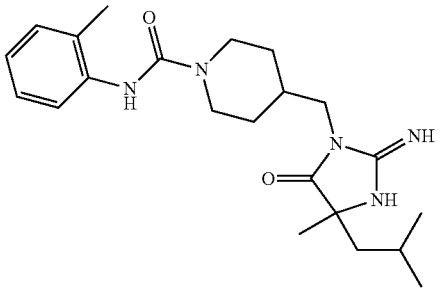
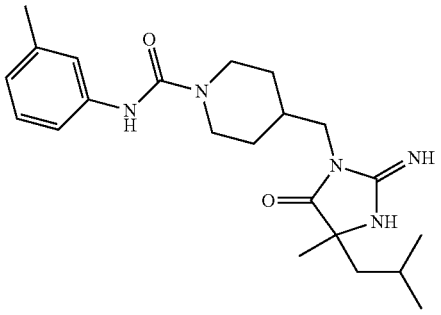
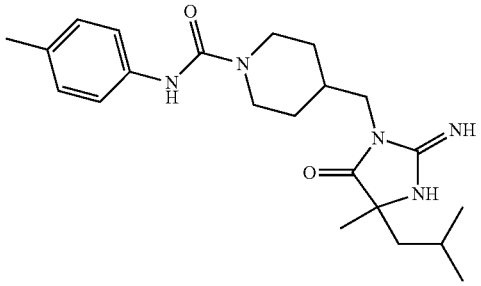
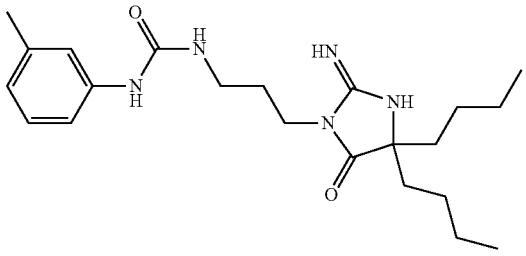
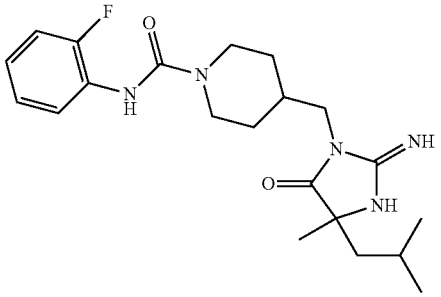
#	Structure	MW	Obs. m/e
1197		399	400
1198		399	400
1199		399	400
1200		401	402
1201		403	404

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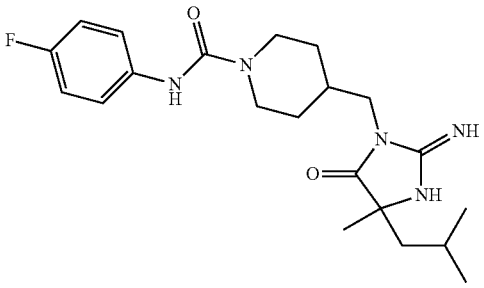
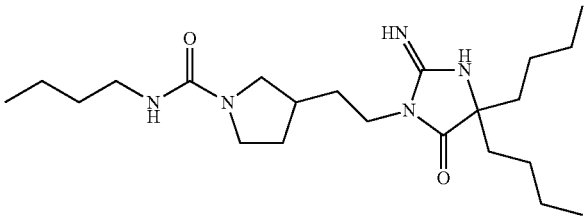
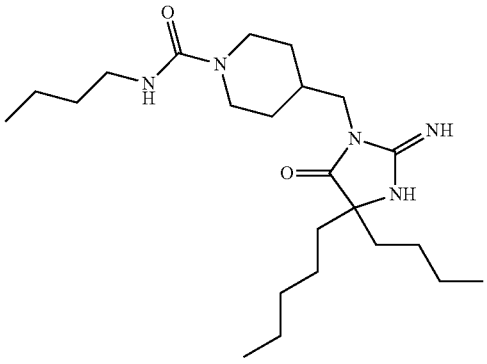
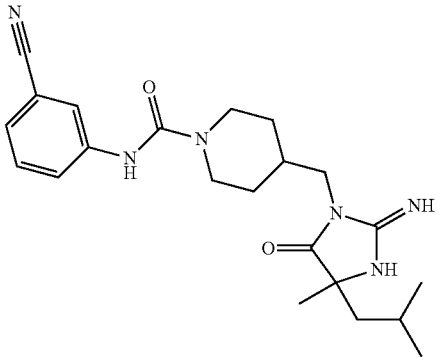
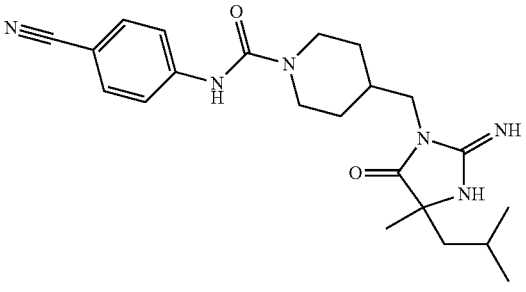
#	Structure	MW	Obs. m/e
1202		403	404
1203		407	408
1204		407	408
1205		410	411
1206		410	411

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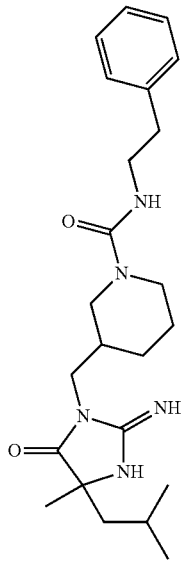
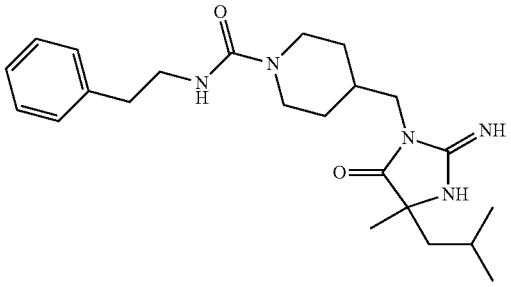
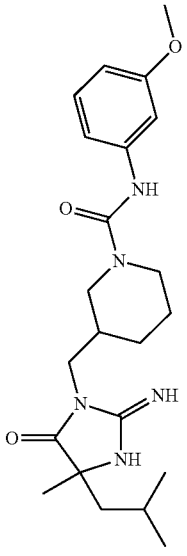
#	Structure	MW	Obs. m/e
1207		413	414
1208		413	414
1209		415	416

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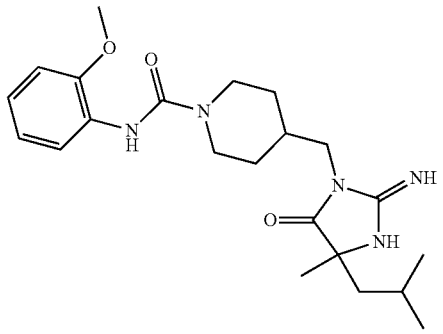
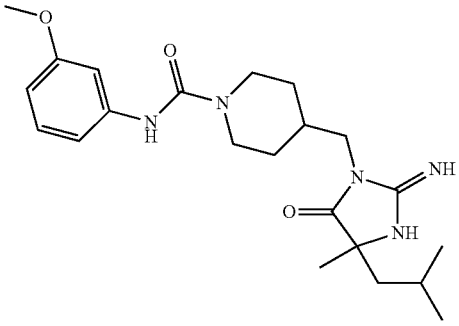
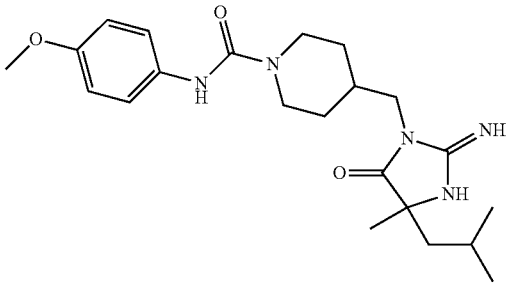
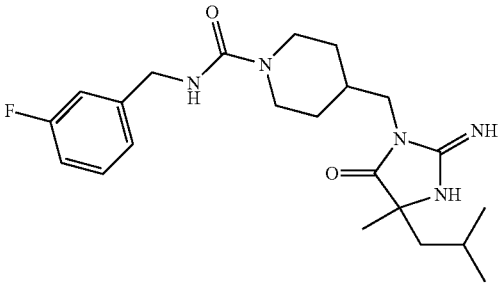
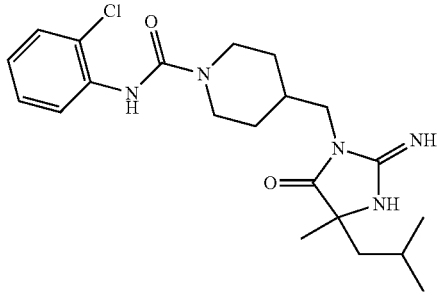
#	Structure	MW	Obs. m/e
1210		415	416
1211		415	416
1212		415	416
1213		417	418
1214		419	420

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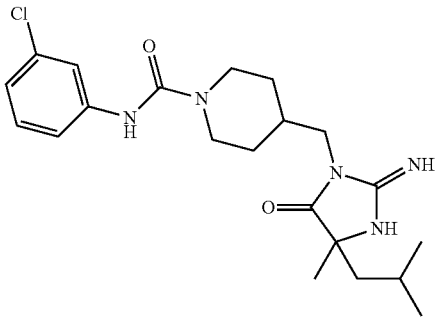
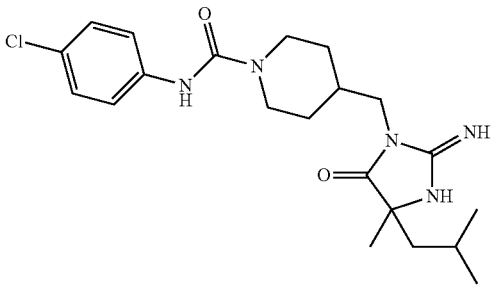
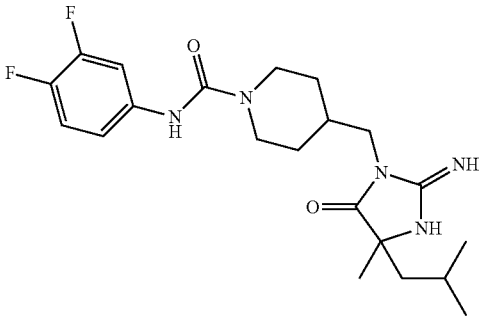
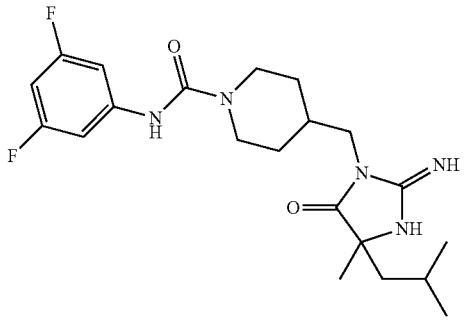
#	Structure	MW	Obs. m/e
1215		419	420
1216		419	420
1217		421	422
1218		421	422

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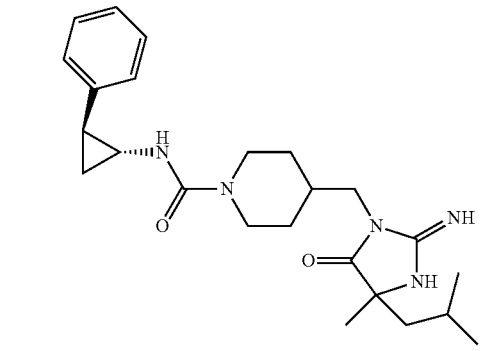
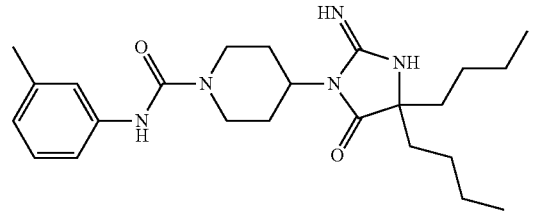
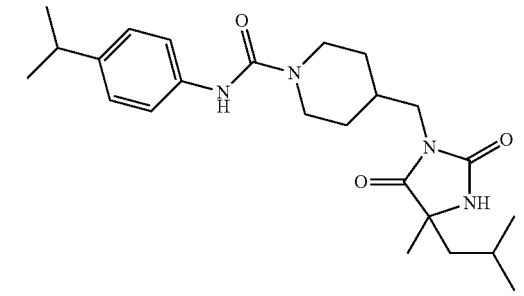
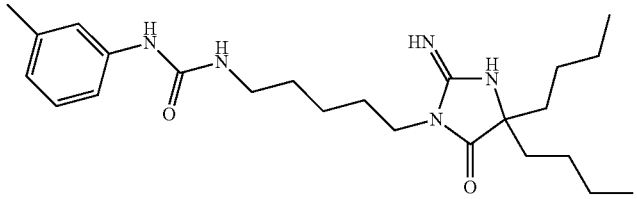
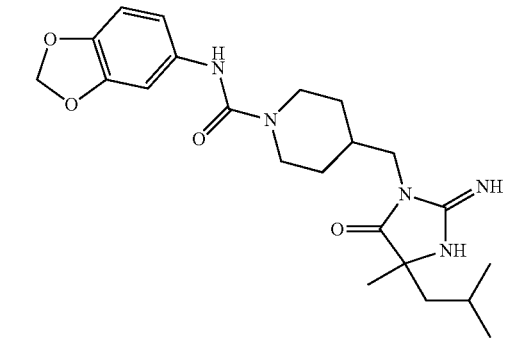
#	Structure	MW	Obs. m/e
1219		425	426
1220		427	428
1221		427	428
1222		429	430
1223		429	430

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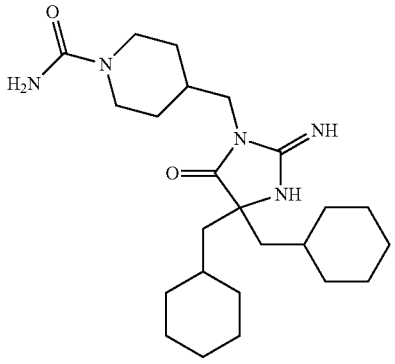
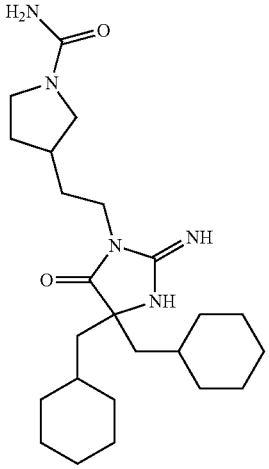
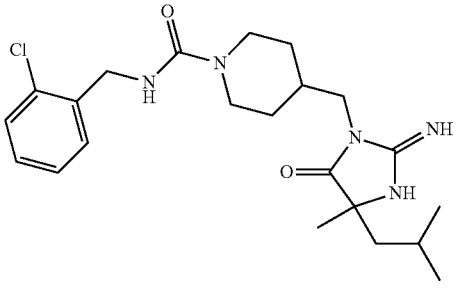
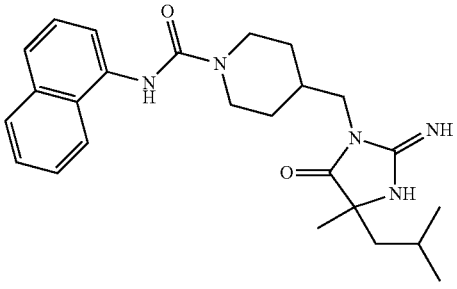
#	Structure	MW	Obs. m/e
1224		431	432
1225		431	432
1226		433	434
1227		435	436

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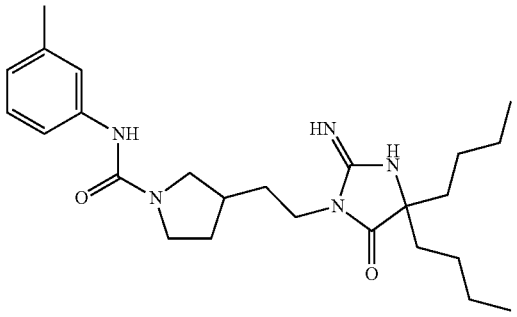
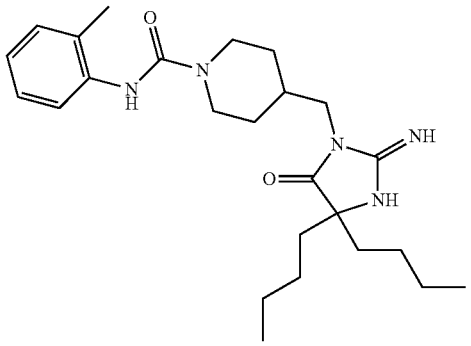
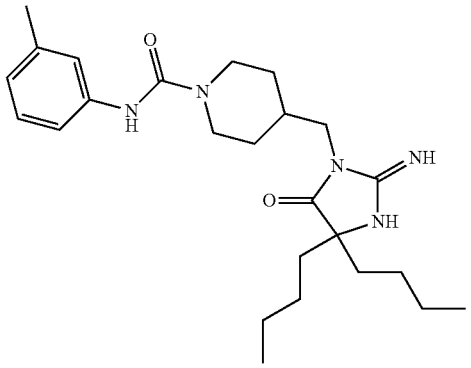
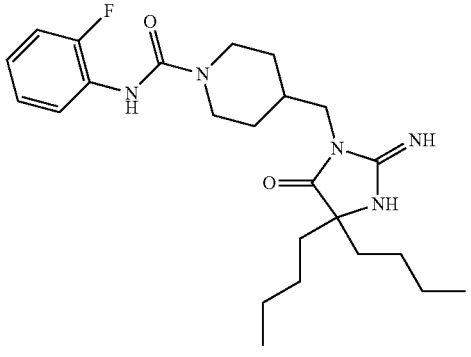
#	Structure	MW	Obs. m/e
1228		441	442
1229		441	442
1230		441	442
1231		445	446

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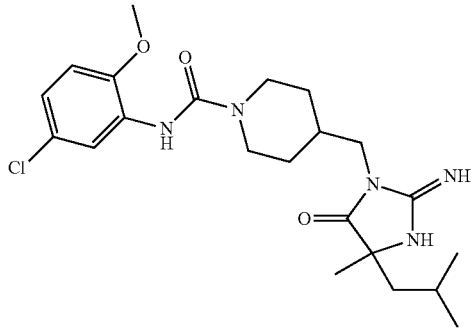
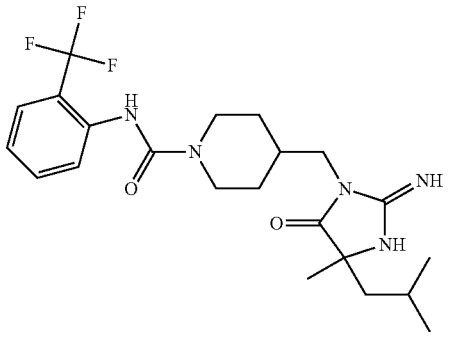
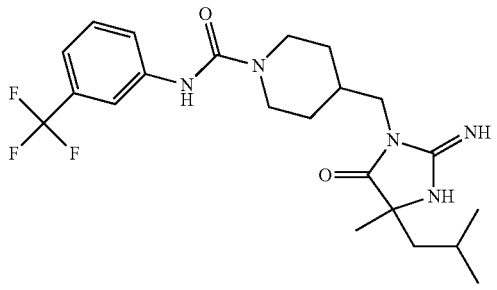
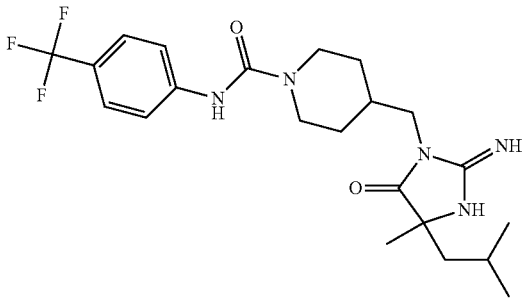
#	Structure	MW	Obs. m/e
1232		449	450
1233		453	454
1234		453	454
1235		453	454

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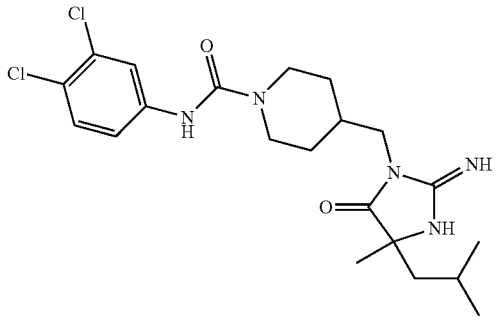
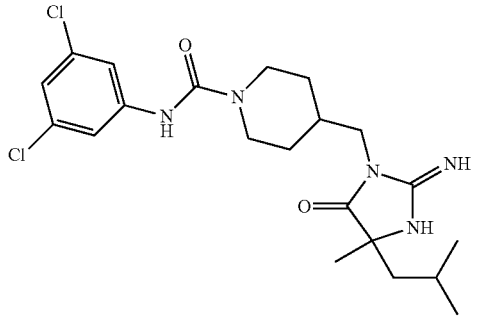
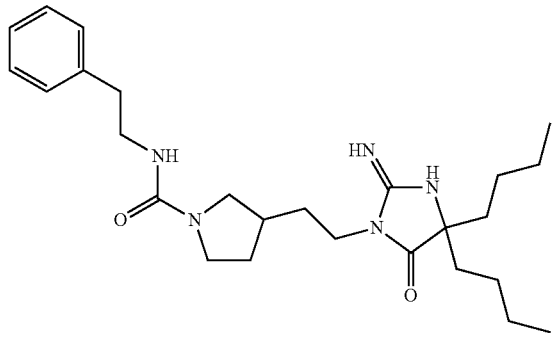
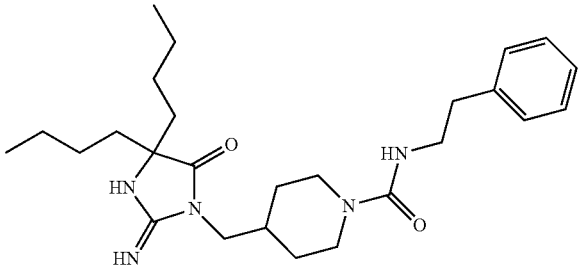
#	Structure	MW	Obs. m/e
1236		453	454
1237		453	454
1238		455	456
1239		455	456

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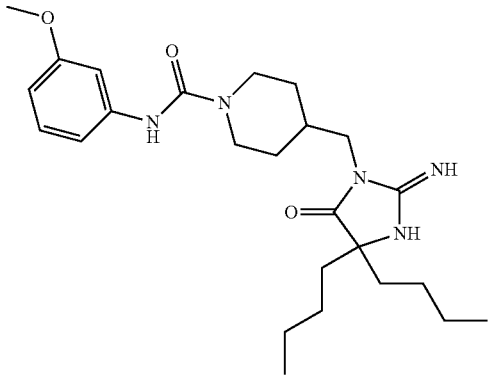
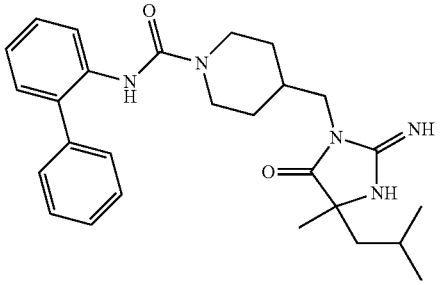
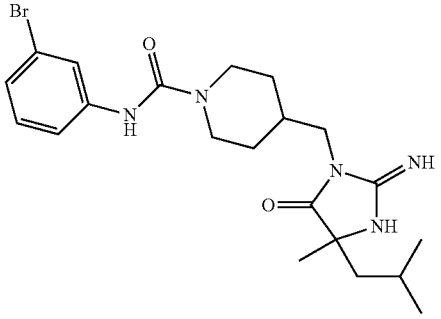
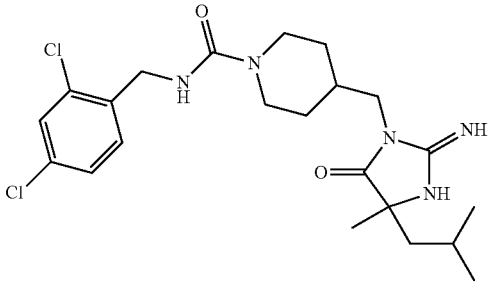
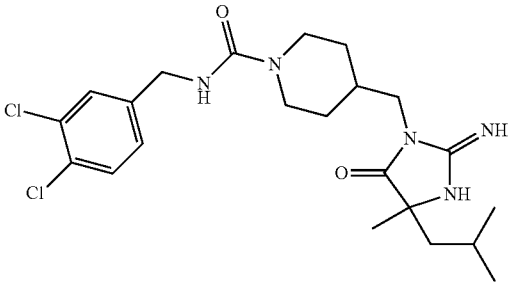
#	Structure	MW	Obs. m/e
1240		457	458
1241		461	462
1242		463	464
1243		467	468
1244		467	468

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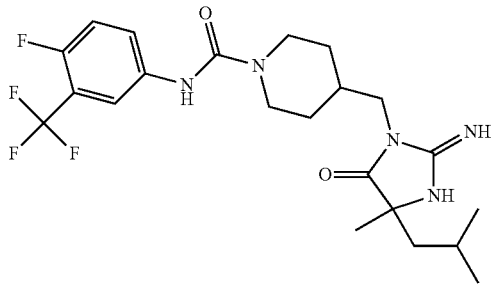
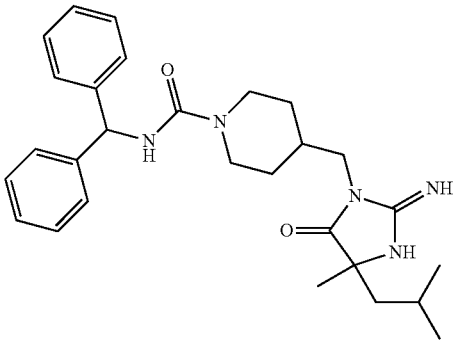
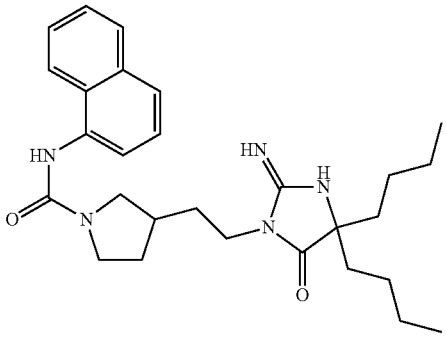
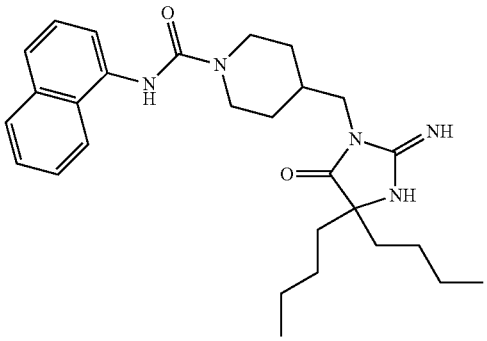
#	Structure	MW	Obs. m/e
1245		471	472
1246		475	476
1247		477	478
1248		477	478

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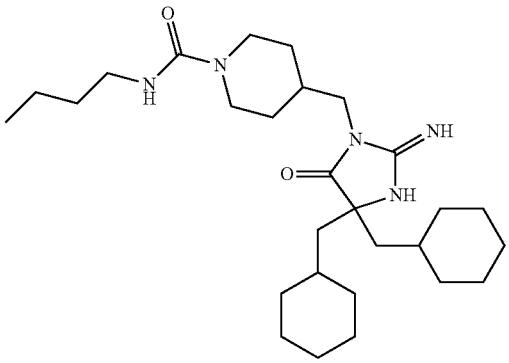
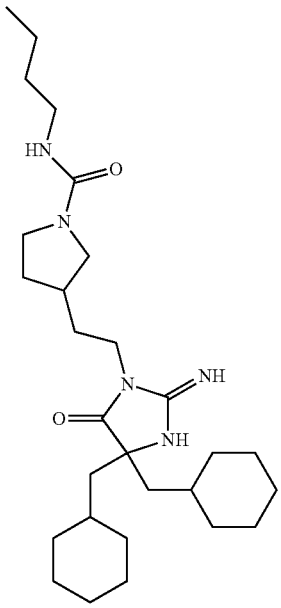
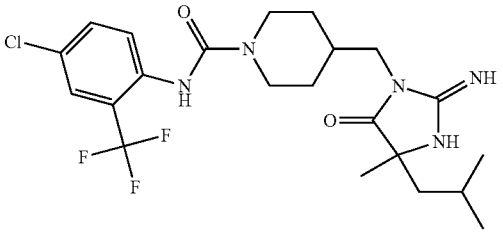
#	Structure	MW	Obs. m/e
1249		487	488
1250		487	488
1251		487	488

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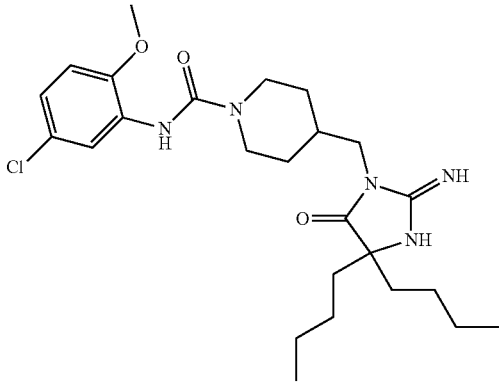
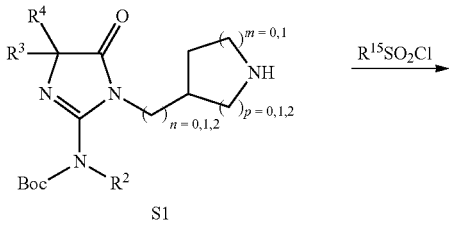
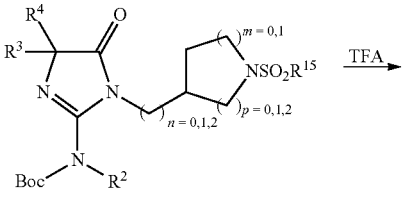
#	Structure	MW	Obs. m/e
1252		491	492

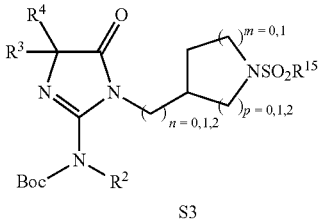
Method S



S1



S2



S3

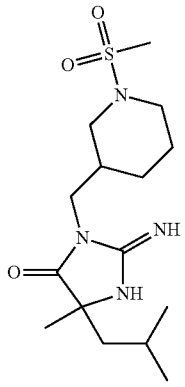
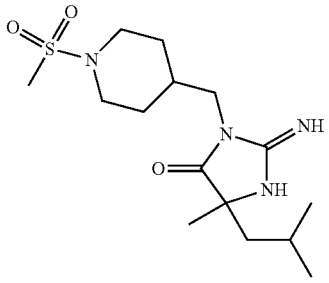
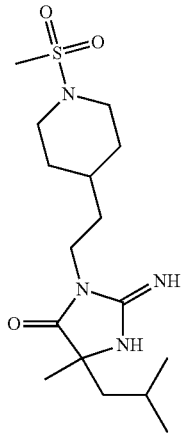
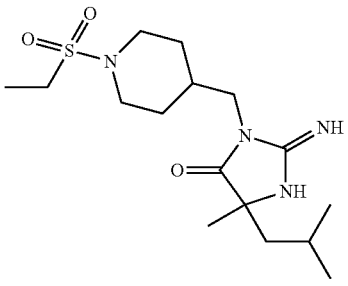
Method S, Step 1.

A solution of S1 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=iBu) (0.010 g) in acetonitrile (0.85 mL) and dichloroethane (0.15 mL) was put into a microtiter plate followed by addition of DIPEA-MP resin (0.030 g, 4 eq) and phenylsulfonyl chloride in dioxane (1 M, 45 μL, 0.045 mmol. The well was capped and shaken for 18 h before it was filtered and residue washed with acetonitrile (0.5 mL). The combined solution was treated with Trisamine resin (0.040 g, 6 eq., 4.23 mmol/g) and Isocyanate resin (0.060 g, 3 equiv., 1.53 mmol/g) and shaken for 18 h before the mixture was filtered and the solvent removed to give S2 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=iBu and R^{15}=Ph).

Method S, Step 2.

Procedure similar to Method Q, step 6 was used for the transformation of S2 to S3 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu and R^{15}=Ph).

The following compounds were prepared using similar methods:

#	Structure	MW	Obs. m/e
1253		344	345
1254		344	345
1255		358	359
1256		358	359

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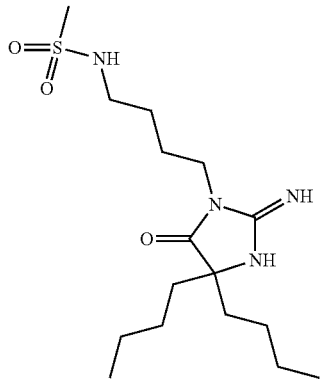
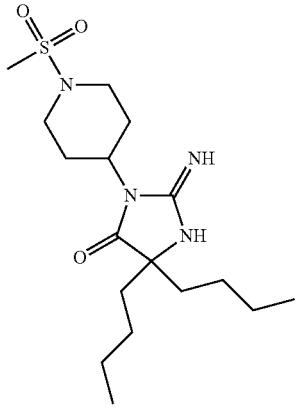
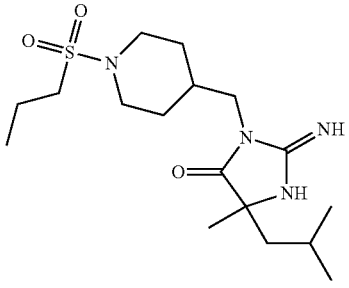
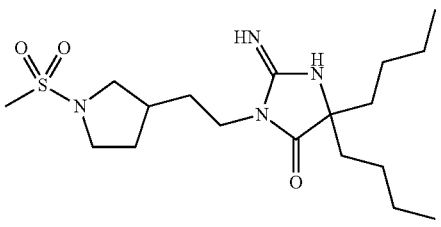
#	Structure	MW	Obs. m/e
1257		360	361
1258		372	373
1259		372	373
1260		386	387

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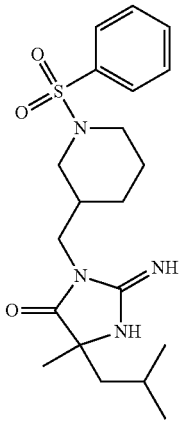
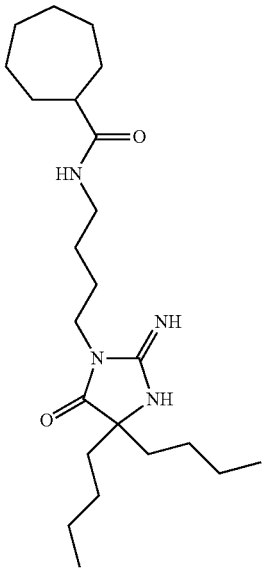
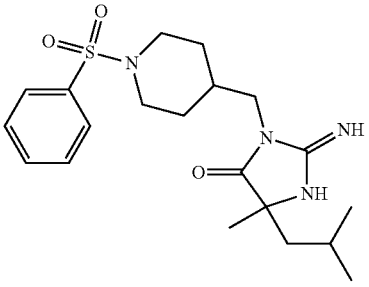
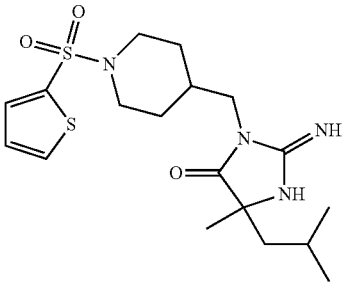
#	Structure	MW	Obs. m/e
1261		406	407
1262		406	407
1263		406	407
1264		412	413

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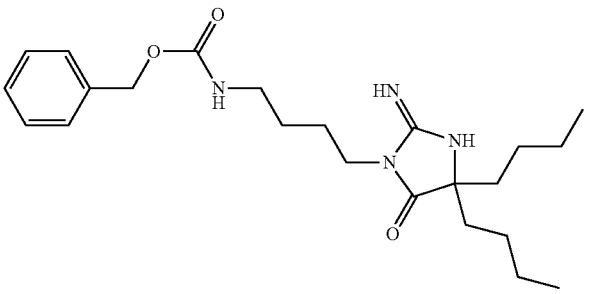
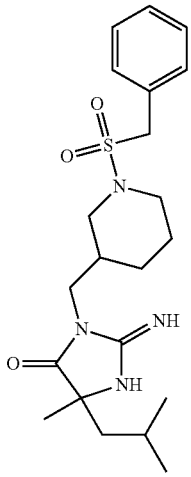
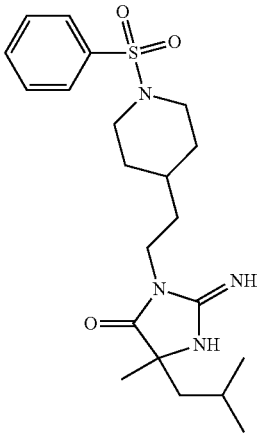
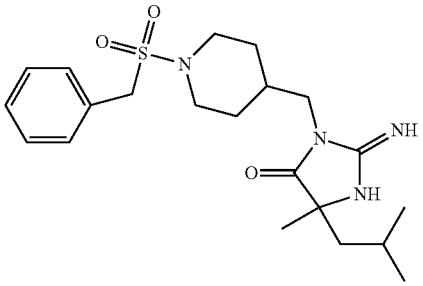
#	Structure	MW	Obs. m/e
1265		416	417
1266		420	421
1267		420	421
1268		420	421

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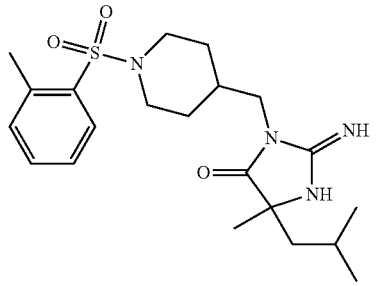
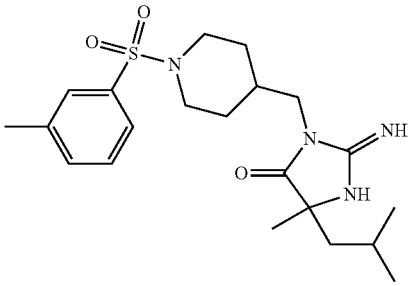
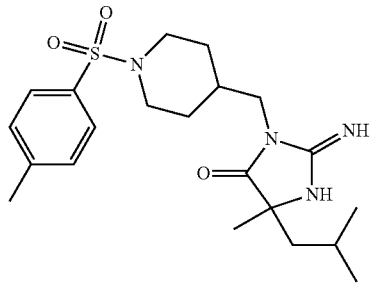
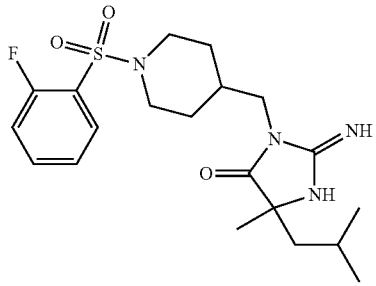
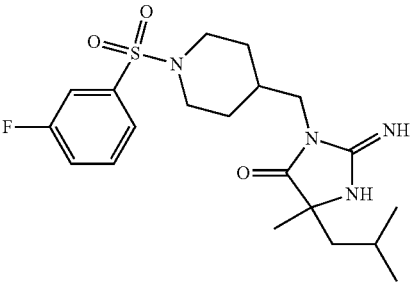
#	Structure	MW	Obs. m/e
1269		420	421
1270		420	421
1271		420	421
1272		424	425
1273		424	425

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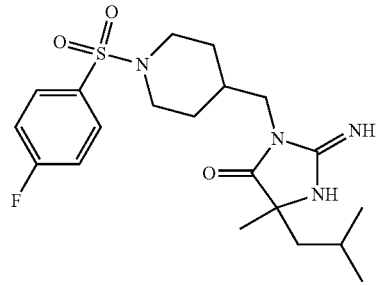
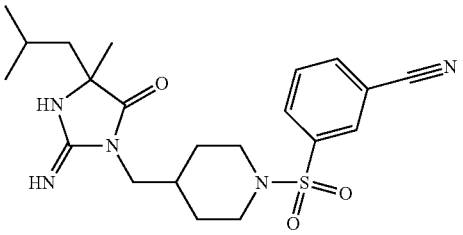
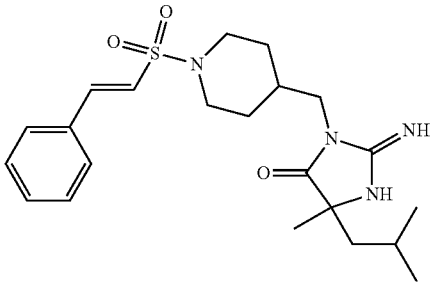
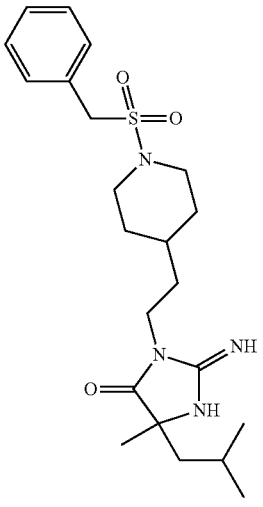
#	Structure	MW	Obs. m/e
1274		424	425
1275		431	432
1276		432	433
1277		434	435

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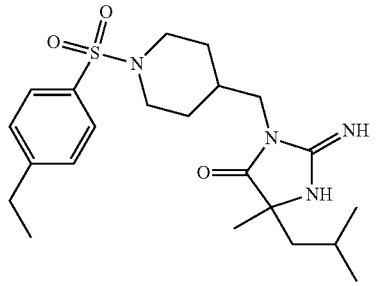
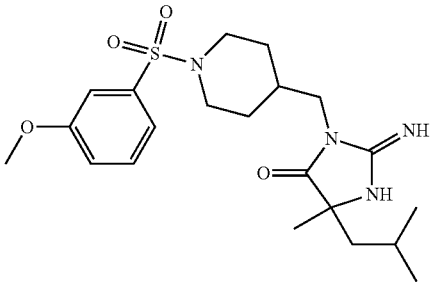
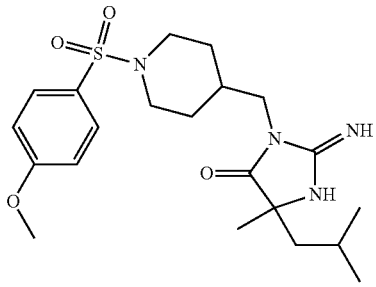
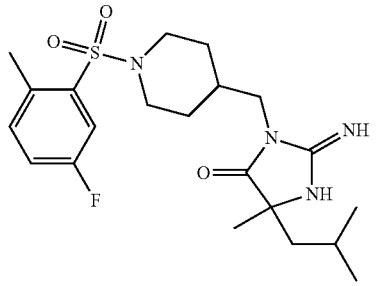
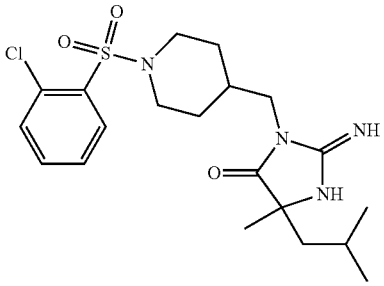
#	Structure	MW	Obs. m/e
1278		434	435
1279		436	437
1280		436	437
1281		438	439
1282		440	441

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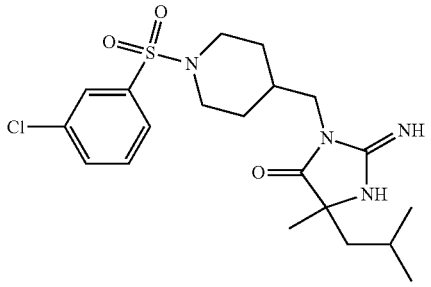
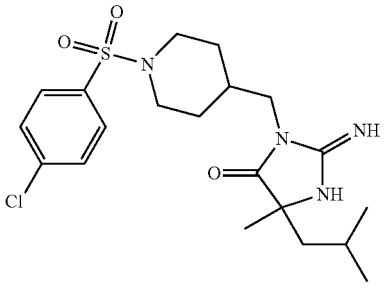
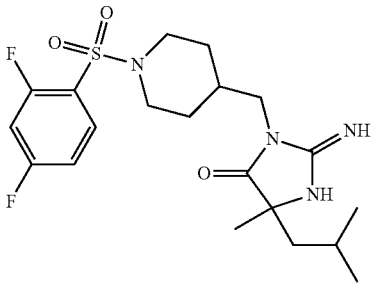
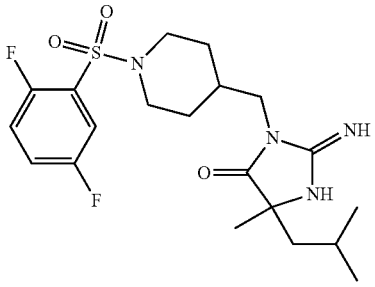
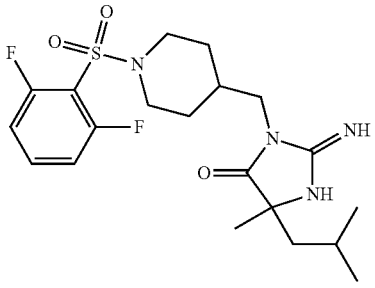
#	Structure	MW	Obs. m/e
1283		440	441
1284		440	441
1285		442	443
1286		442	443
1287		442	443

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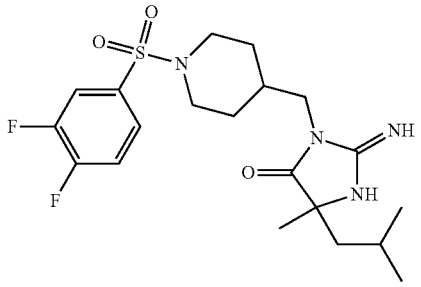
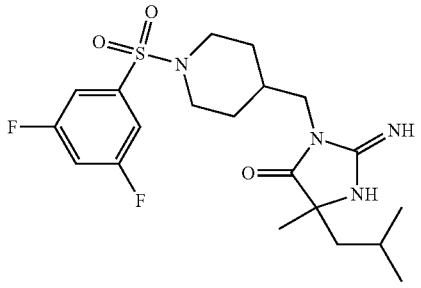
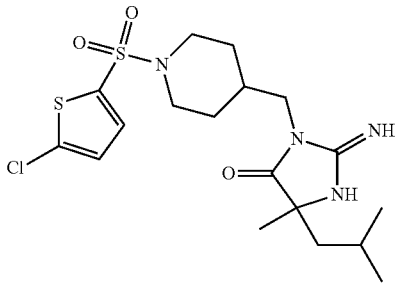
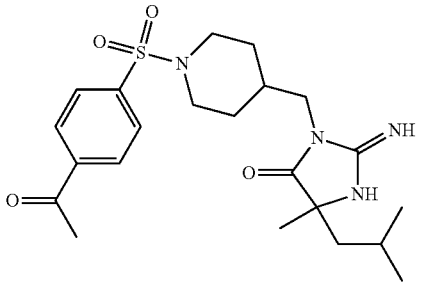
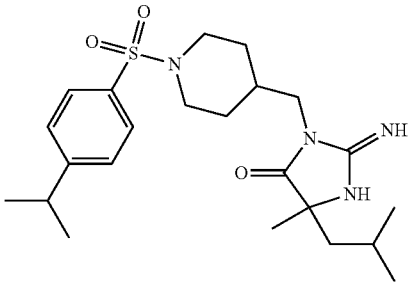
#	Structure	MW	Obs. m/e
1288		442	443
1289		442	443
1290		446	447
1291		448	449
1292		448	449

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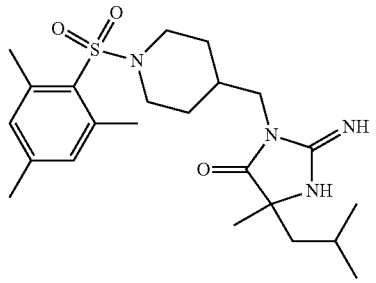
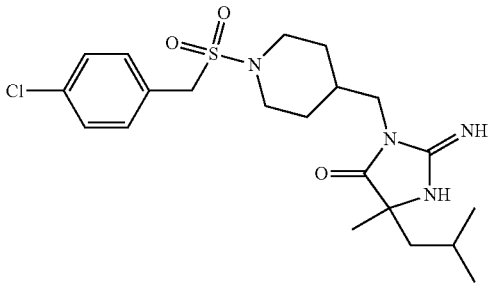
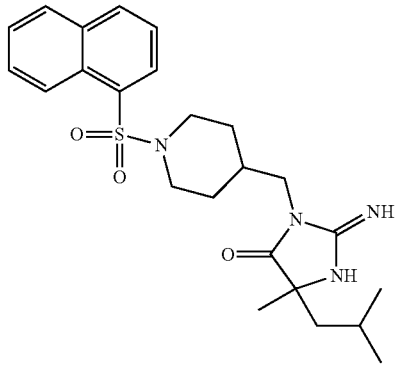
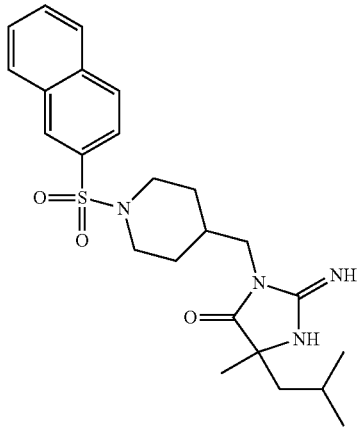
#	Structure	MW	Obs. m/e
1293		448	449
1294		454	455
1295		456	457
1296		456	457

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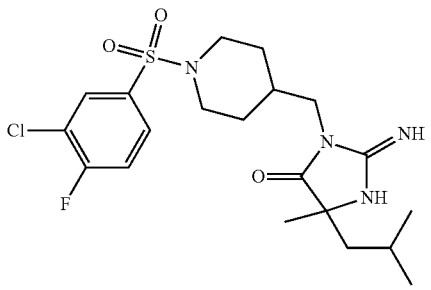
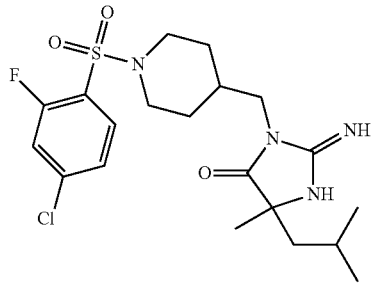
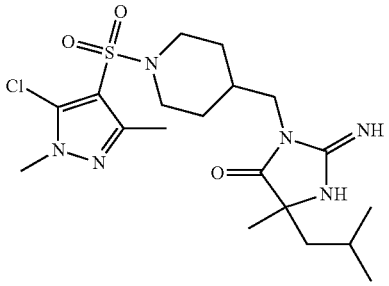
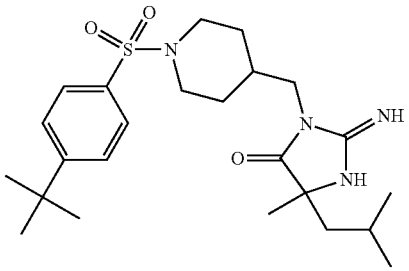
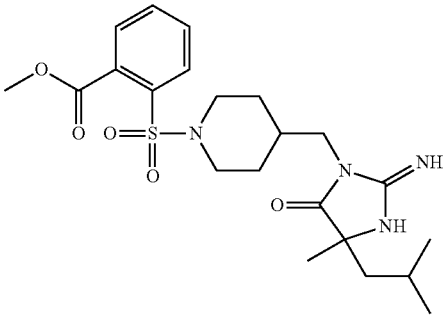
#	Structure	MW	Obs. m/e
1297		458	459
1298		458	459
1299		458	459
1300		462	463
1301		464	465

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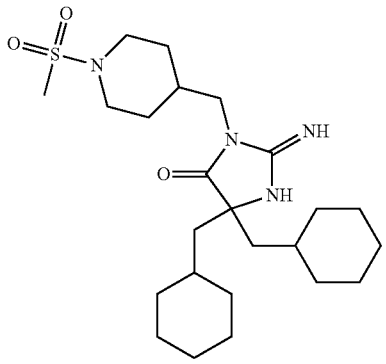
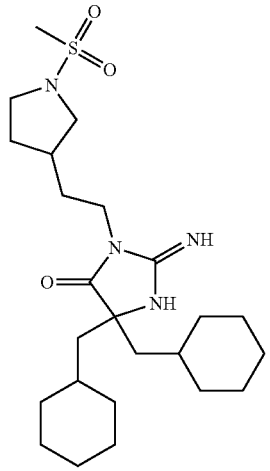
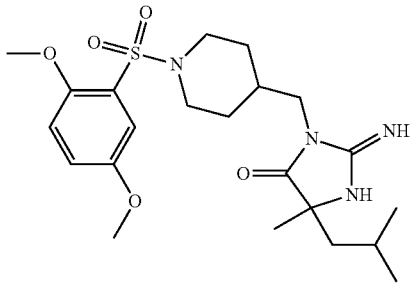
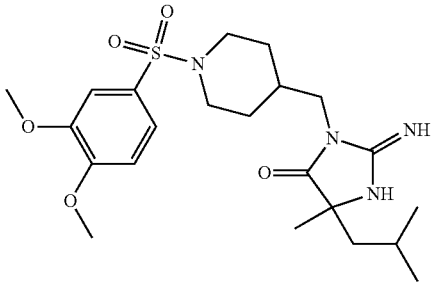
#	Structure	MW	Obs. m/e
1302		466	467
1303		466	467
1304		466	467
1305		466	467

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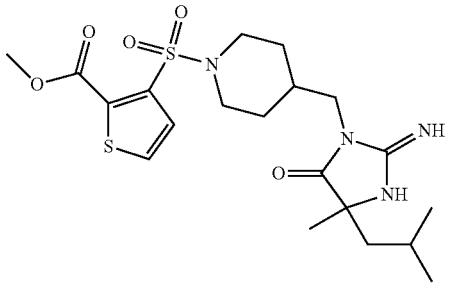
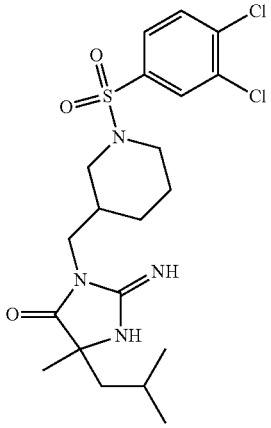
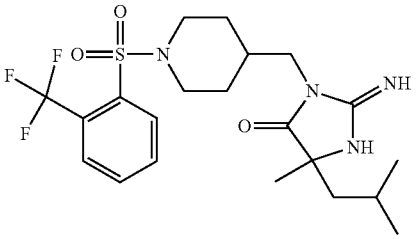
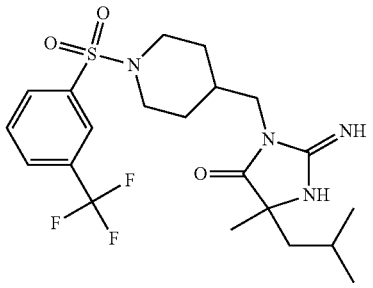
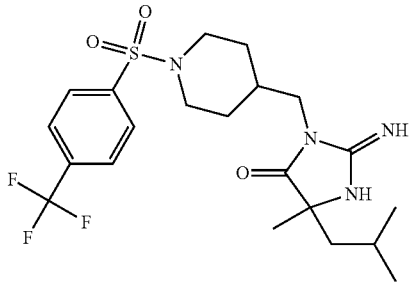
#	Structure	MW	Obs. m/e
1306		470	471
1307		474	475
1308		474	475
1309		474	475
1310		474	475

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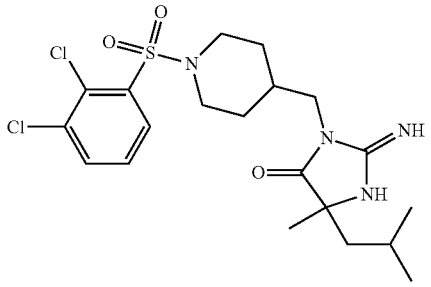
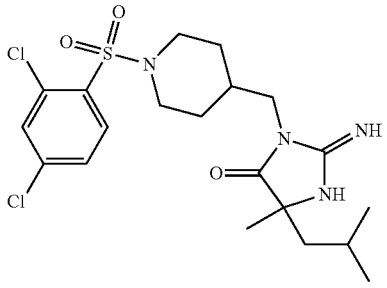
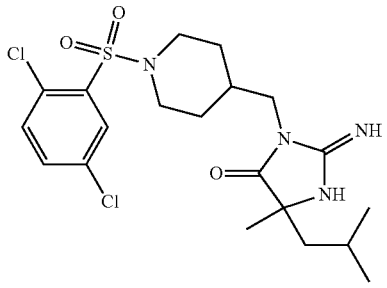
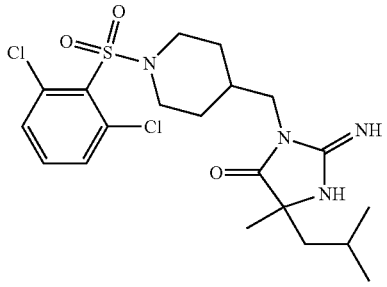
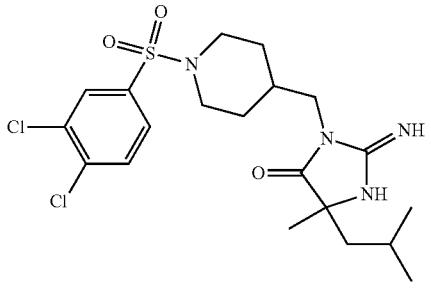
#	Structure	MW	Obs. m/e
1311		474	475
1312		474	475
1313		474	475
1314		474	475
1315		474	475

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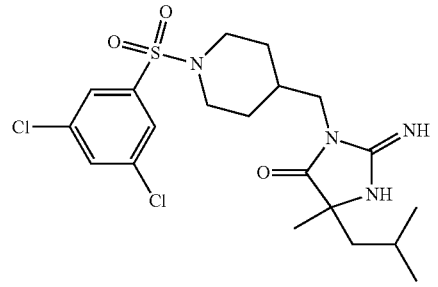
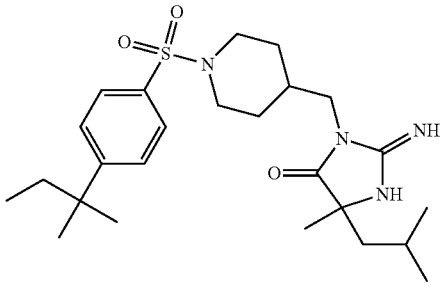
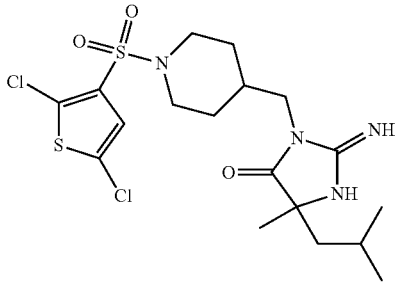
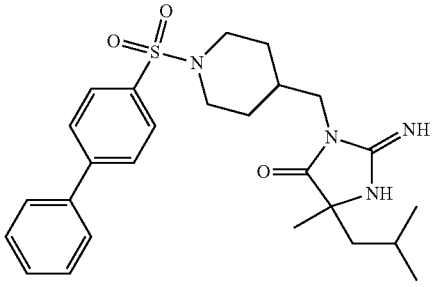
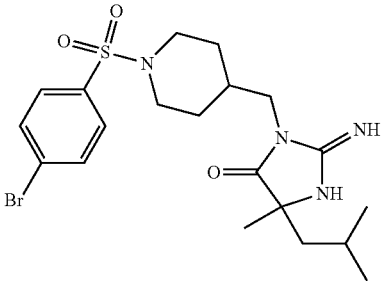
#	Structure	MW	Obs. m/e
1316		474	475
1317		476	477
1318		480	481
1319		482	483
1320		484	485

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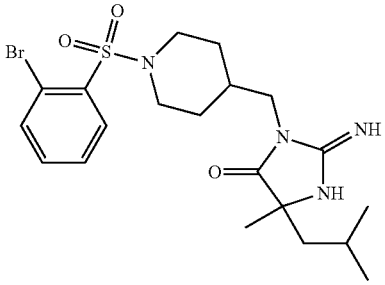
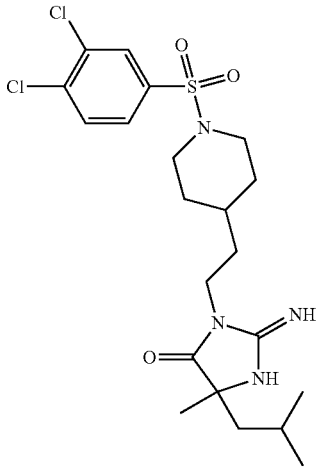
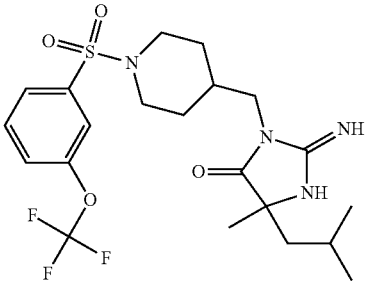
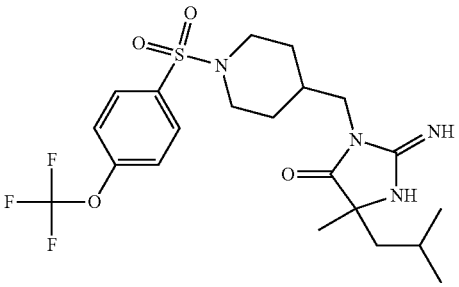
#	Structure	MW	Obs. m/e
1321		484	485
1322		488	489
1323		490	491
1324		490	491

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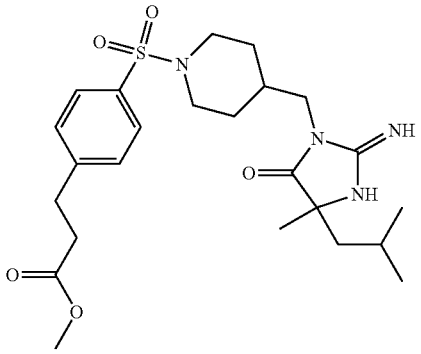
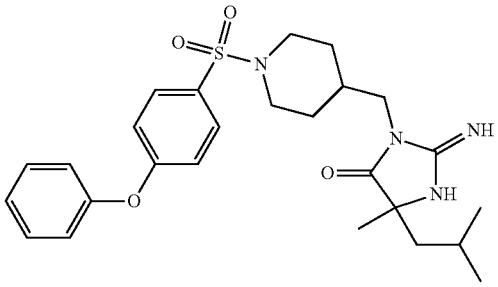
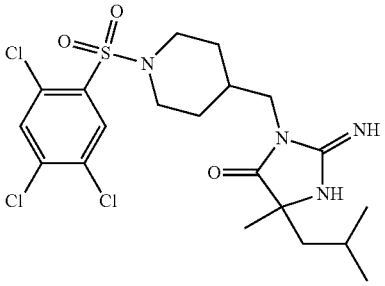
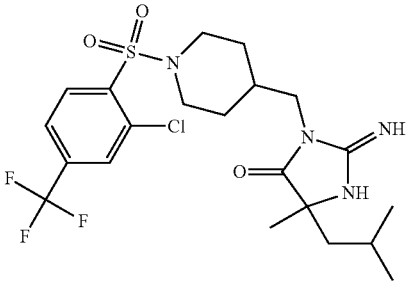
#	Structure	MW	Obs. m/e
1325		492	493
1326		498	499
1327		508	509
1328		508	509

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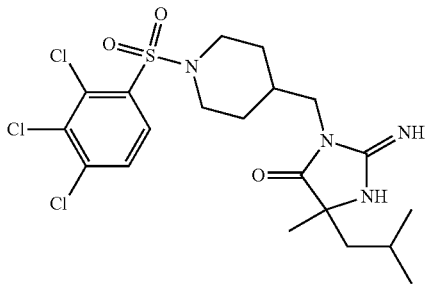
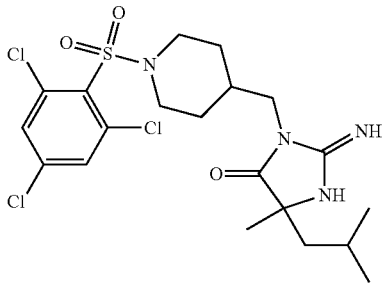
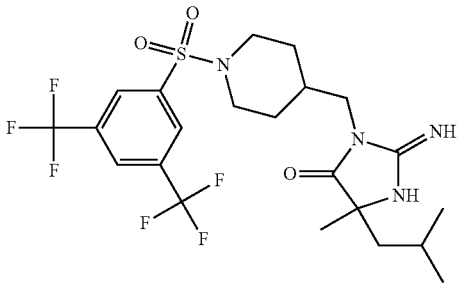
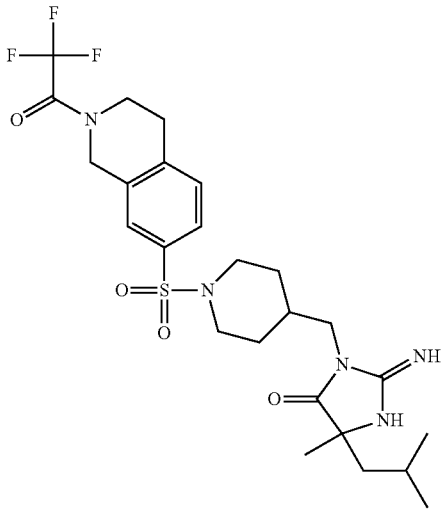
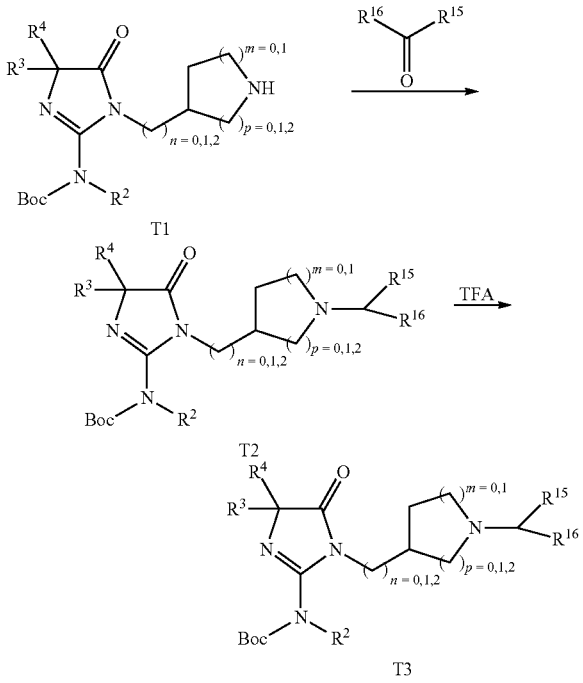
#	Structure	MW	Obs. m/e
1329		508	509
1330		508	509
1331		542	543
1332		557	558

Method T



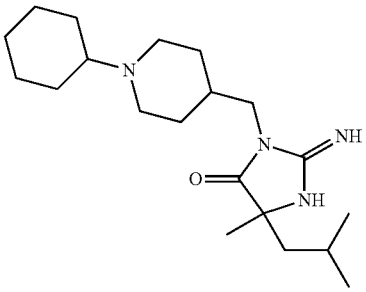
Method T, Step 1.

To a microtiter plate well containing 1 ml solution of T1 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=iBu) in DCM (0.010 g) and $R^{15}C(O)R^{16}$ (5 equiv, R^{15}=H, R^{16}=Ph) was added Sodium cyanoborohydride in dichloroethane (14.3 mg/mL, 2 equiv.). The well was capped and shaken for 20 h before MP-TsOH Resin (100 mg, 1.29 mmol/g) was added to the well followed by additional MP-TsOH resin (50 mg) after 2 h. After the mixture was shaken for another 1 h, the mixture was filtered and the resin washed with dichloroethane (1 mL) (3×), then MeOH (1 mL) (2×). The resin was treated with 7N ammonia in MeOH (1 mL) for 30 min (2×) followed by filtration and evaporation of solvent to give T2 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu and R^{15}=Ph and R^{16}=H).

Method T, Step 2.

Procedure similar to Method Q, step 6 was used for the transformation of T2 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=iBu and R^{15}=Ph and R^{16}=H) to T3 (n=1, p=2, m=1, R^2=H, R^3=Me; R^4=^{i}Bu and R^{15}=Ph and R^{16}=H).

The following compounds were prepared using similar methods:

#	Structure	MW	Obs. m/e
1333		348	349

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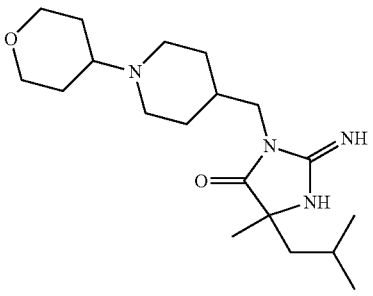
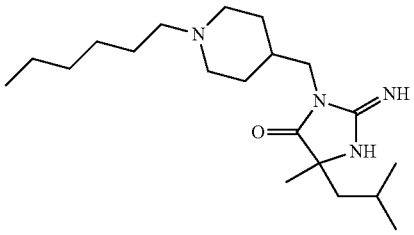
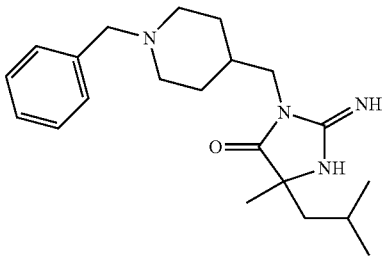
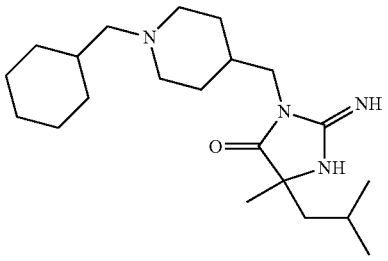
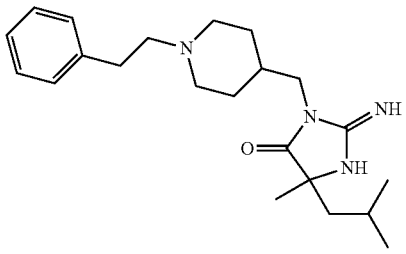
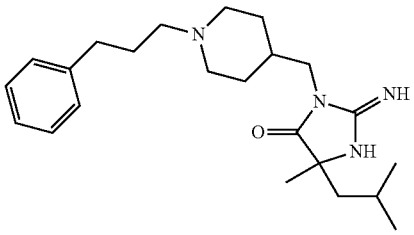
#	Structure	MW	Obs. m/e
1334		350	351
1335		350	351
1336		356	357
1337		362	363
1338		370	371
1339		384	385

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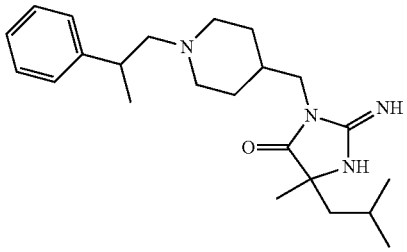
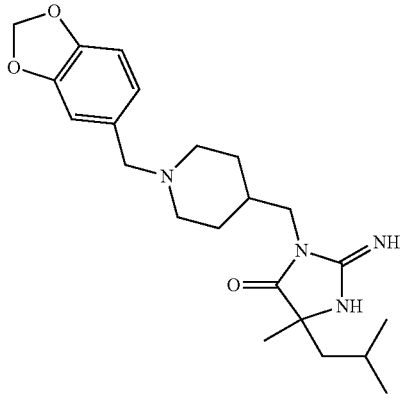
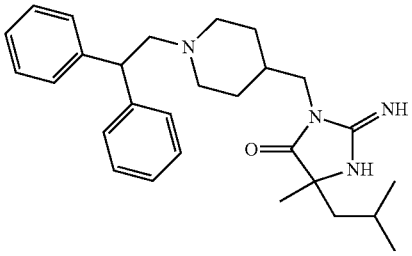
#	Structure	MW	Obs. m/e
1340		384	385
1341		400	401
1342		446	447

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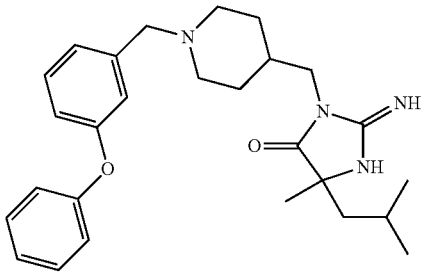
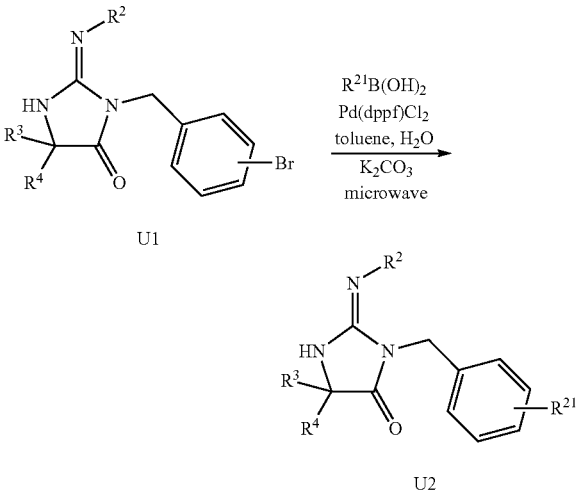
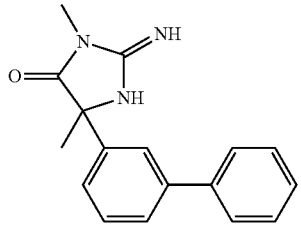
#	Structure	MW	Obs. m/e
1343		448	449

Method U



In a microwave vial was charged U1 (R^2=H; R^3=i-Bu, R^4=Me) (0.025 g) in toluene (4 mL), potassium carbonate (0.035 g), $Pd(dppf)Cl_2$ (0.020 g). water (0.02 mL) and $R^{21}B(OH)_2$ (R^{21}=m-Methoxyphenyl) (3 eq.) were placed. The vial was placed in a microwave for 10 min. at 150° C. The reaction mixture was diluted with dichloromethane and extracted with 2.5N NaOH. The dried ($MgSO_4$) dichloromethane solution was concentrated in vacua to give a brown residue which was purified via a RP Prep LCMS system to give product U2 (R^2=H; R^3=^{i}Bu: R^4=Me; R^{21}=m-methoxyphenyl).

The following compounds were prepared using similar methods:

#	Structure	MW	Obs. m/e
1344		279	280

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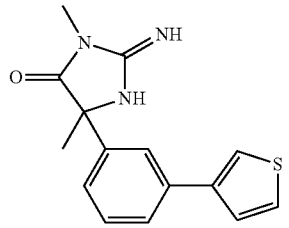
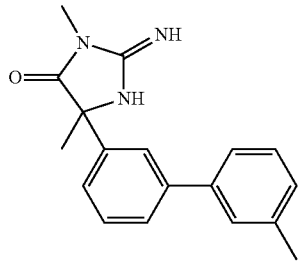
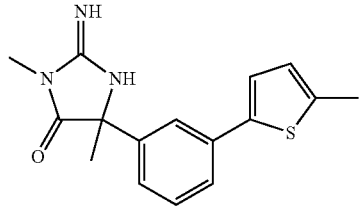
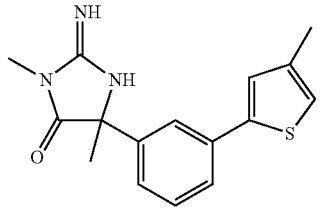
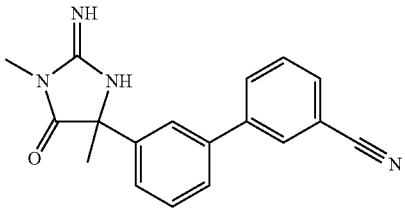
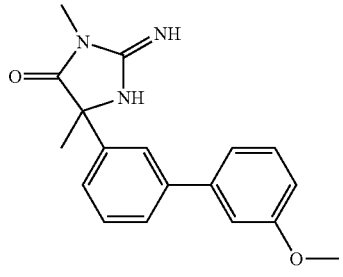
#	Structure	MW	Obs. m/e
1345		285	286
1346		293	294
1347		299	300
1348		299	300
1349		304	305
1350		309	310

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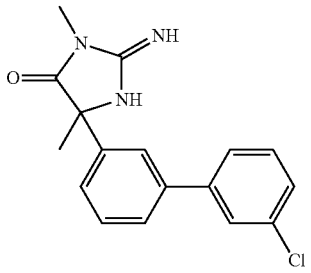
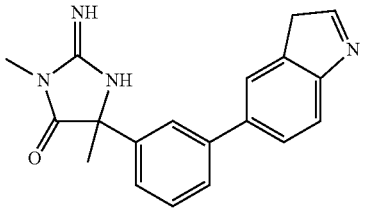
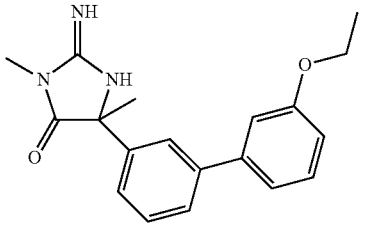
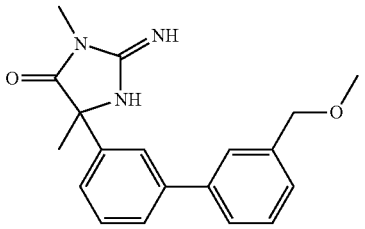
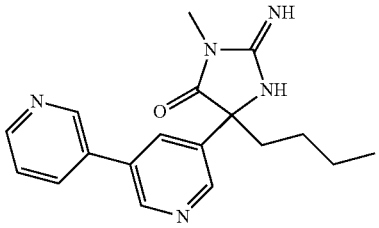
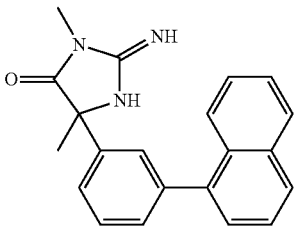
#	Structure	MW	Obs. m/e
1351		313	314
1352		318	319
1353		323	324
1354		323	324
1355		323	324
1356		329	330

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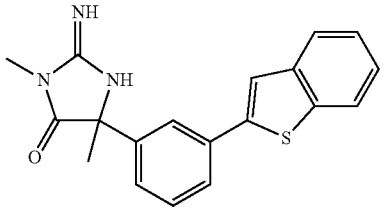
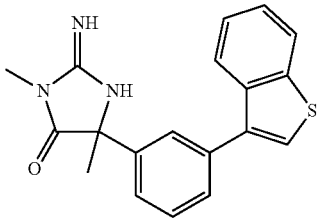
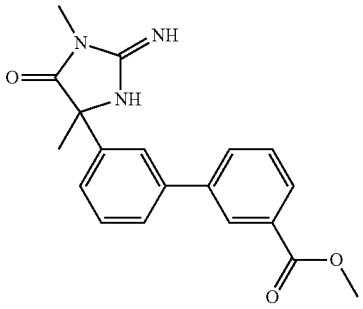
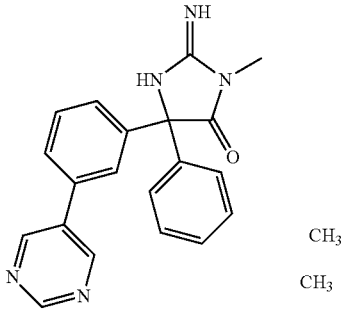
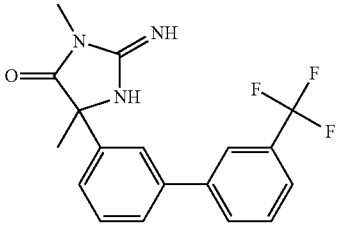
#	Structure	MW	Obs. m/e
1357		335	336
1358		335	336
1359		337	338
1360		343	344
1361		347	348

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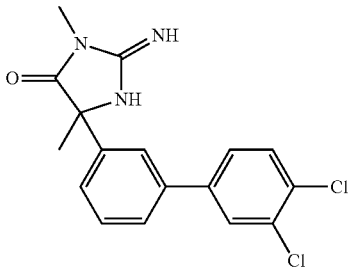
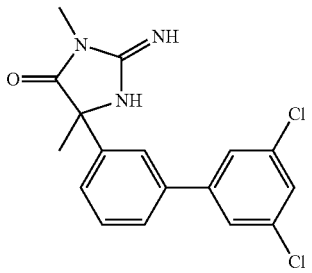
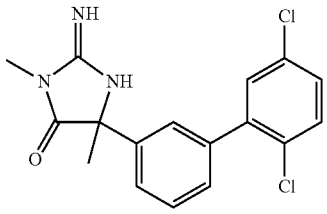
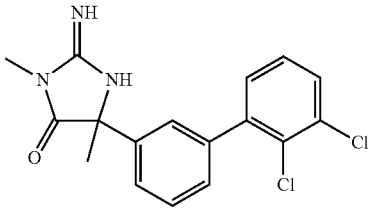
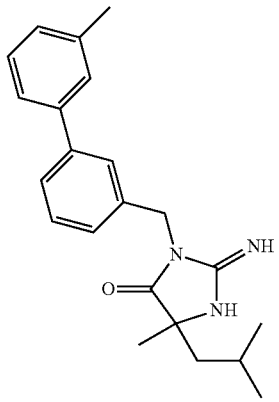
#	Structure	MW	Obs. m/e
1362		347	348
1363		347	348
1364		347	348
1365		347	348
1366		349	350

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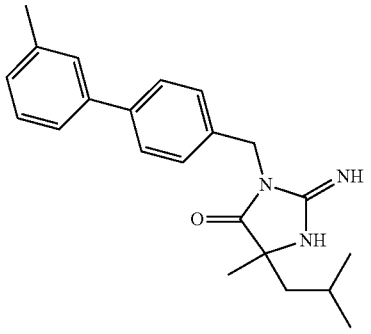
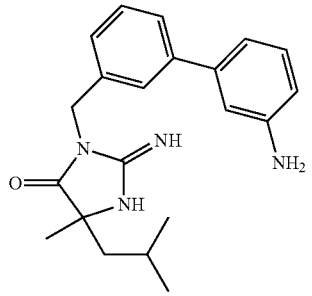
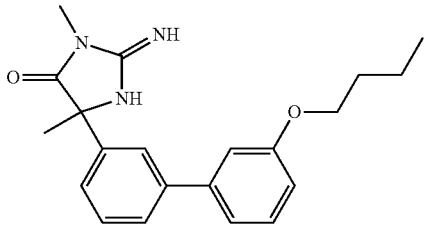
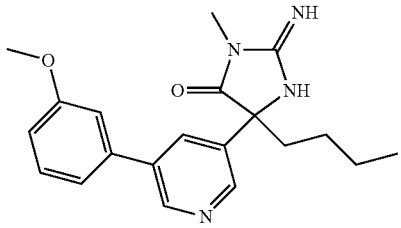
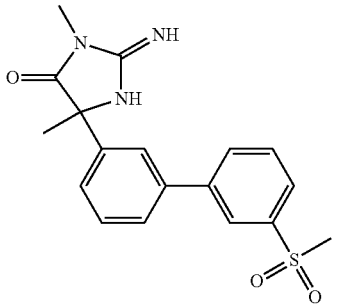
#	Structure	MW	Obs. m/e
1367		349	350
1368		350	351
1369		351	352
1370		352	353
1371		357	358

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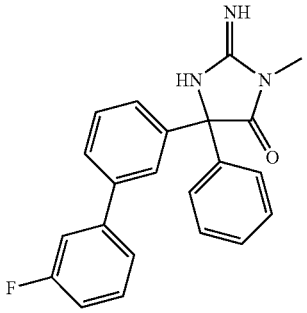
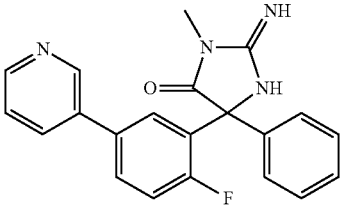
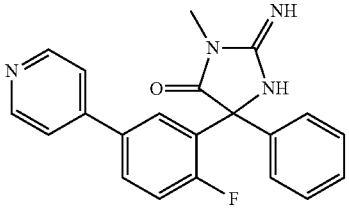
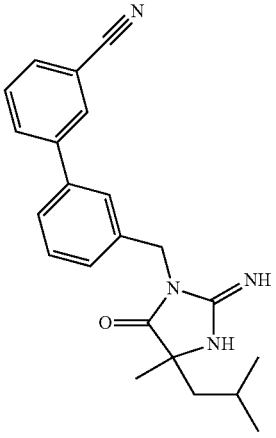
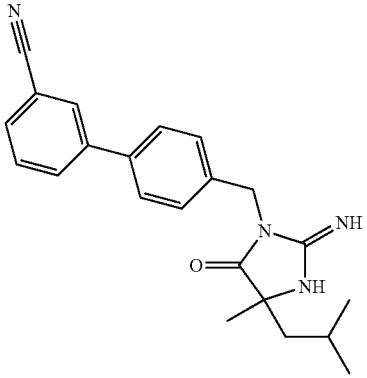
#	Structure	MW	Obs. m/e
1372		359	360
1373		360	361
1374		360	361
1375		360	361
1376		360	361

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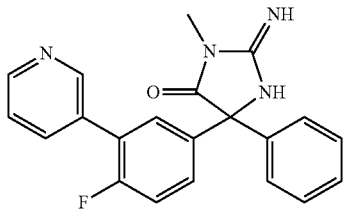
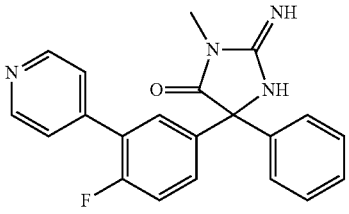
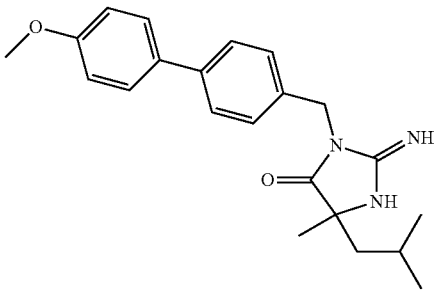
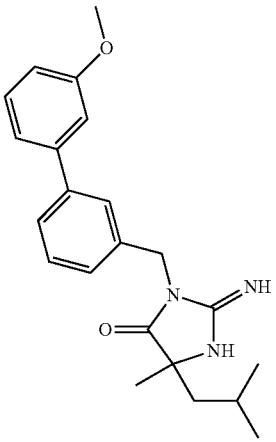
#	Structure	MW	Obs. m/e
1377		360	361
1378		360	361
1379		365	366
1380		365	366

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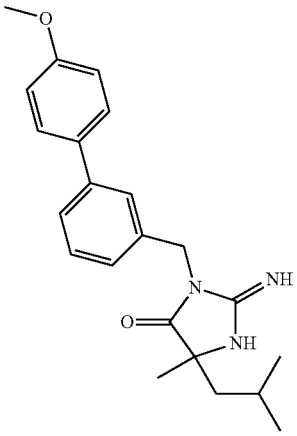
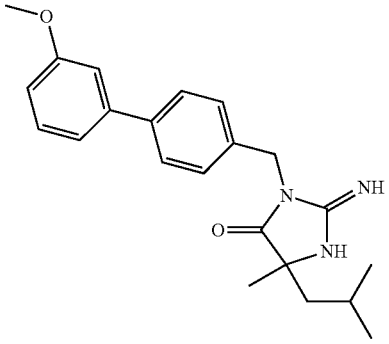
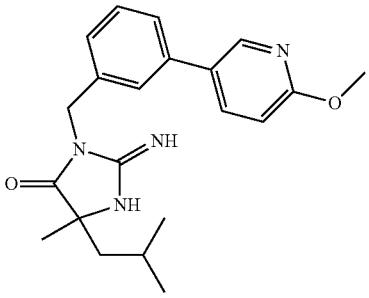
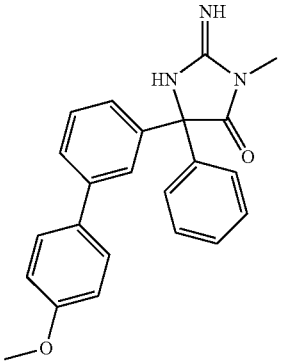
#	Structure	MW	Obs. m/e
1381		365	366
1382		365	366
1383		366	367
1384		371	372

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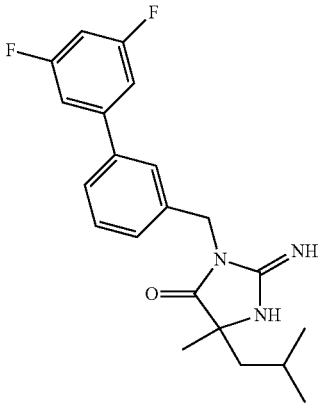
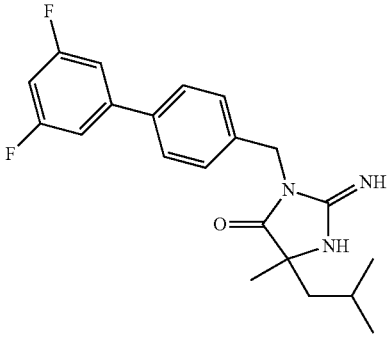
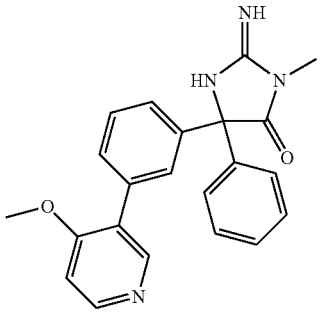
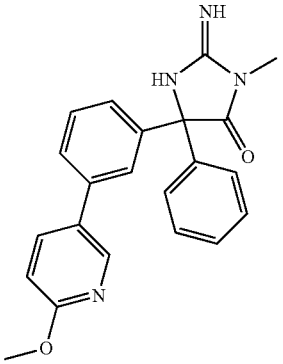
#	Structure	MW	Obs. m/e
1385		371	372
1386		371	372
1387		372	373
1388		372	373

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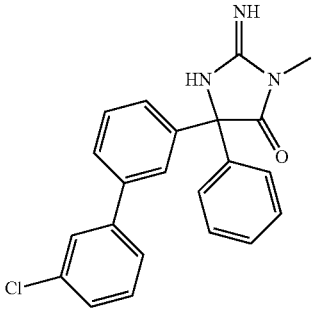
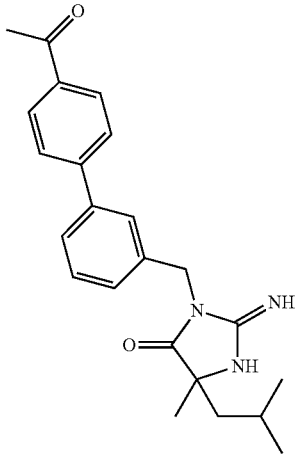
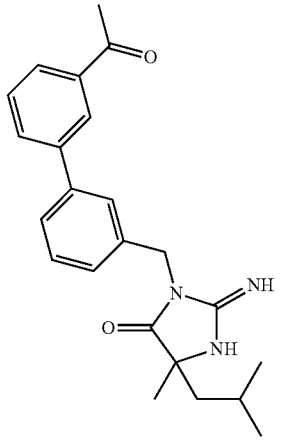
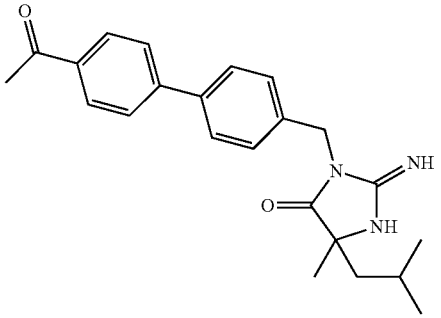
#	Structure	MW	Obs. m/e
1389		375	376
1390		377	378
1391		377	378
1392		377	378

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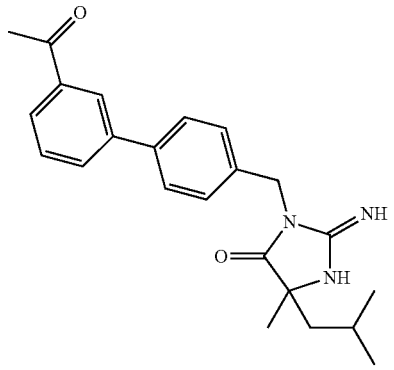
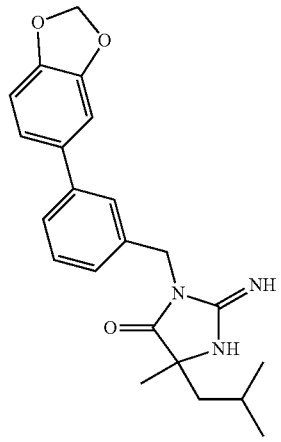
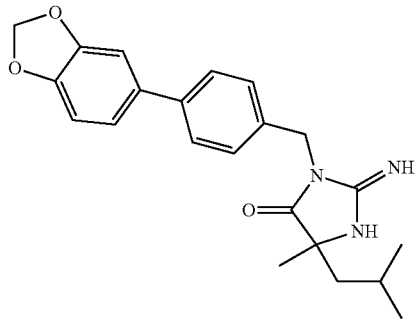
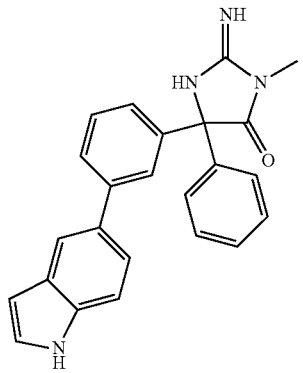
#	Structure	MW	Obs. m/e
1393		377	378
1394		379	380
1395		379	380
1396		380	381

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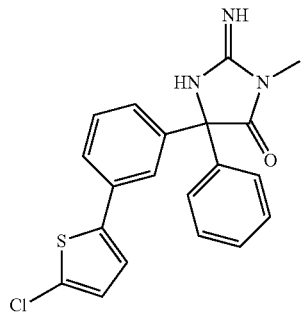
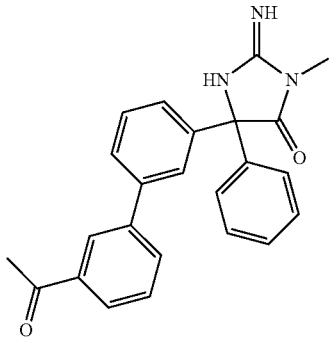
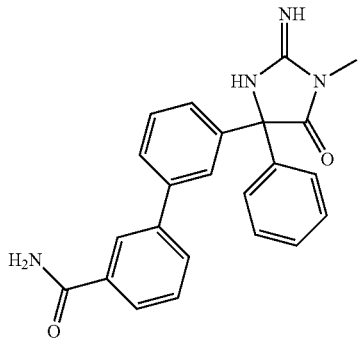
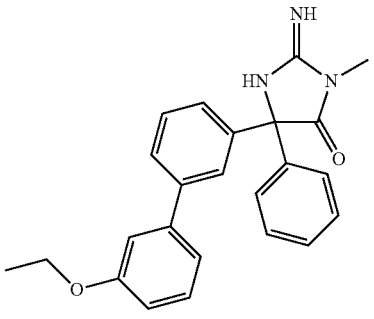
#	Structure	MW	Obs. m/e
1397		381	382
1398		383	384
1399		384	385
1400		385	386

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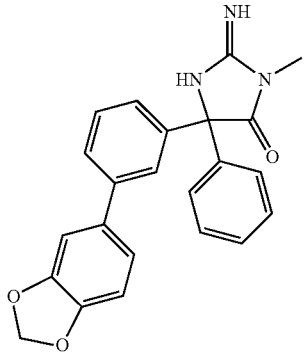
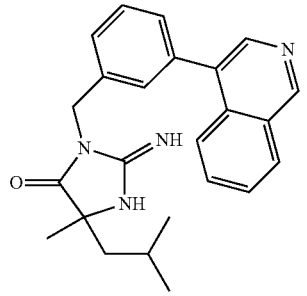
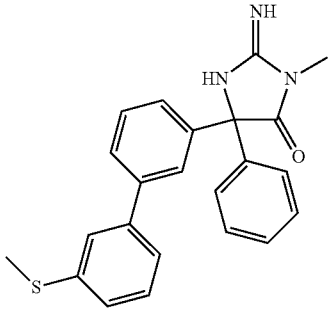
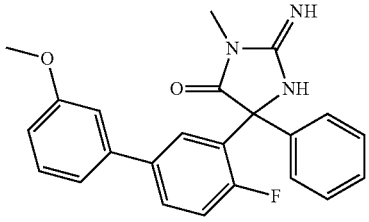
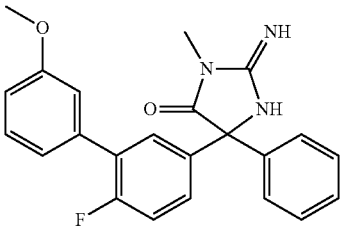
#	Structure	MW	Obs. m/e
1401		385	386
1402		386	387
1403		387	388
1404		389	390
1405		389	390

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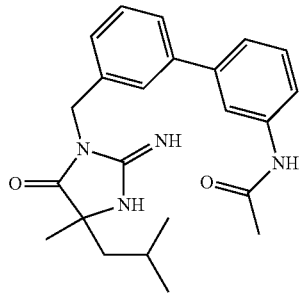
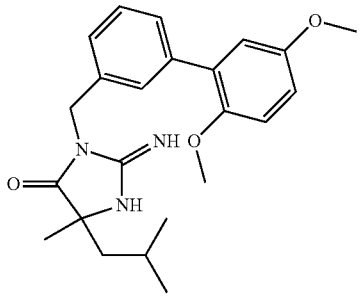
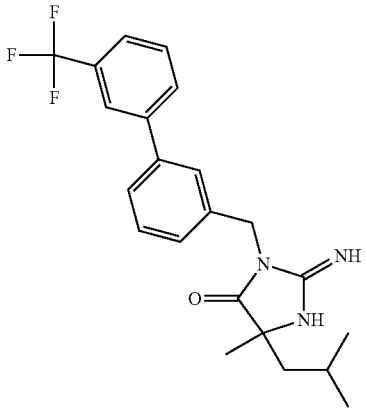
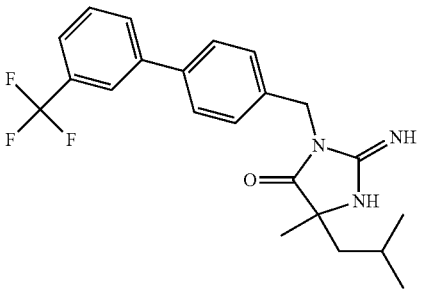
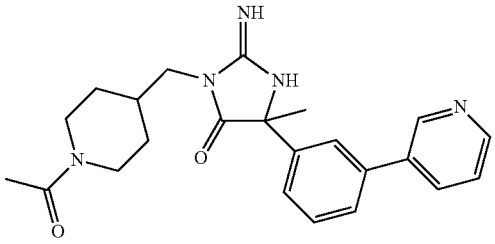
#	Structure	MW	Obs. m/e
1406		392	393
1407		395	396
1408		403	404
1409		403	404
1410		405	406

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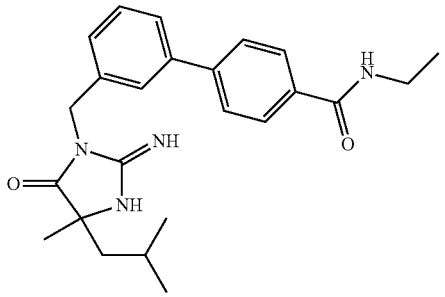
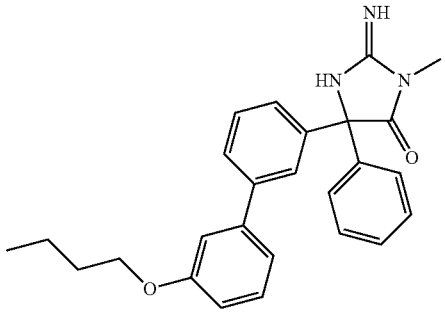
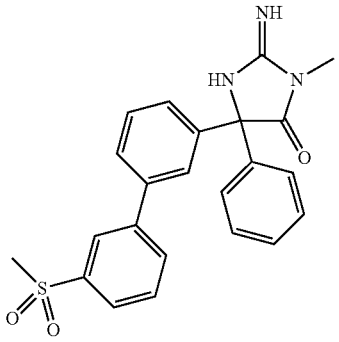
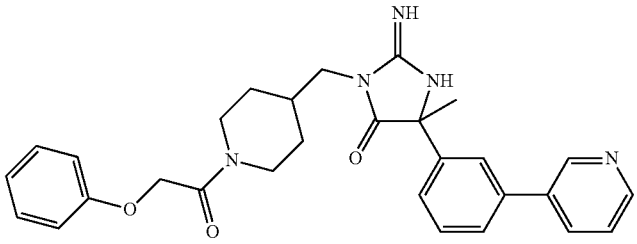
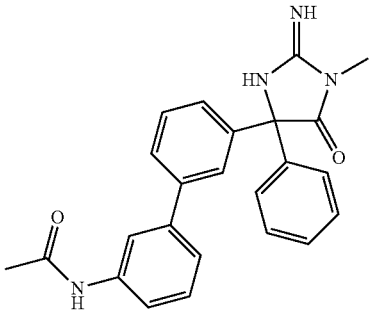
#	Structure	MW	Obs. m/e
1411		406	407
1412		413	414
1413		419	420
1414		497	498
1415		398	TBD

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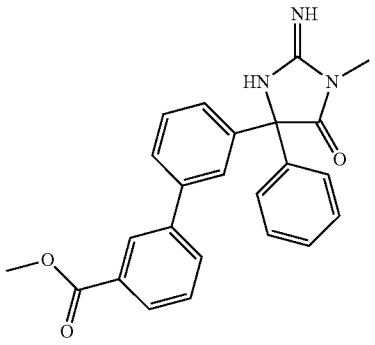
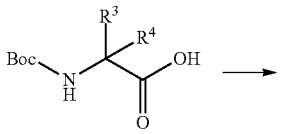
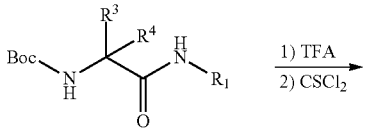
#	Structure	MW	Obs. m/e
1416		399	TBD

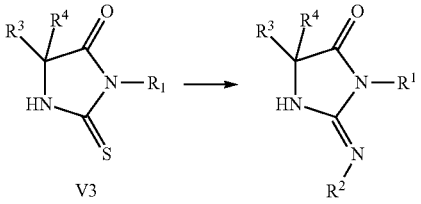
Method V



V1



V2



V3 V4

Method V, Step 1:

Compound V1 (R^3=R^4=Me) (14.76 mmole), EDCI (14.76 mmole), HOAt (14.76 mmole), and DIEA (14.76 mmole) were mixed with 36 ml DCM. This mixture was stirred at RT for 15 min before 3-chlorobenzylamine was added. After the reaction solution was stirred at RT overnight, it was washed with sodium carbonate (3×), water, 1N HCl (4×), and aq sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified on flash column to give the amide product V2 (R^1=3-chlorobenzyl; R^3=R^4=Me).

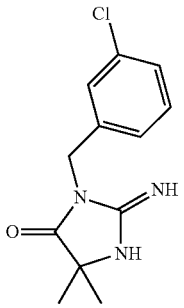
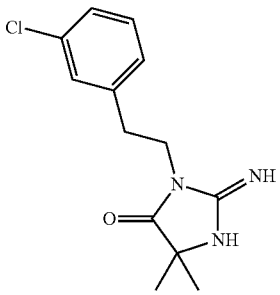
Method V, step 2

Compound V2 (R^1=3-chlorobenzyl; R^3=R^4=Me) (8.33 mmole) was dissolved in 35 ml anhydrous DCM, and cooled to 0-5° C. Thiophosgene (9.16 mmole) in 10 ml DCM was added dropwise under N_2 followed by addition of DIEA (11.96 mmole). The solution was stirred in ice bath for 0.5 h before the reaction mixture was washed with saturated sodium bicarbonate (3×), brine, and dried over anhydrous sodium sulfate. The solvent was evaporated and residue purified on flash column using ethylacetate/hexane to give the thiohydantoin V3 (R^1=3-chlorobenzyl; R^3=R^4=Me).

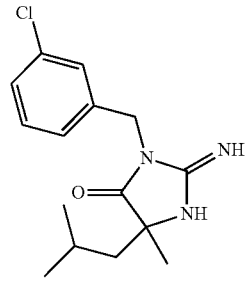
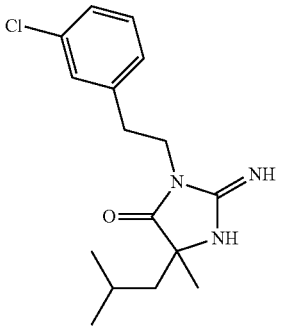
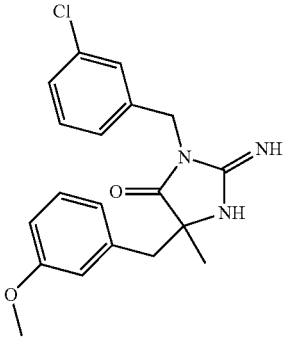
Method V, step 3:

The thiohydantoin V3 (R^1=3-chlorobenzyl; R^3=R^4=Me) was treated with t-butyl hydroperoxide and ammonium hydroxide in MeOH at RT for 48 h to give compound V4 (R^1=3-chlorobenzyl; R^2=H; R^3=R^4=Me).

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e
1417		251	252
1418		265	266

-continued

#	Structure	MW	Obs. m/e
1419		293	294
1420		307	308
1421		357	358

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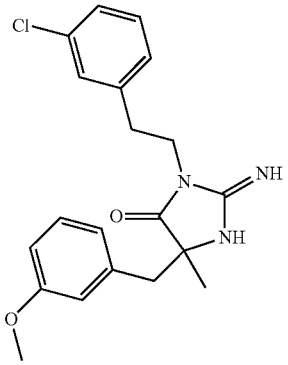
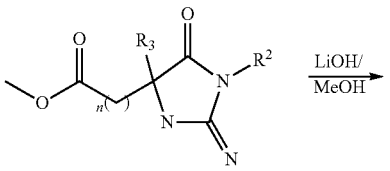
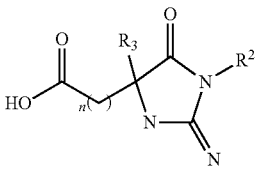
#	Structure	MW	Obs. m/e
1422		371	372

Method W



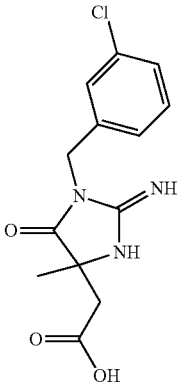
W1



W2

Compound W1 obtained using method A (n=1, R^2=m-Cl-Bn, R^3=Me) was hydrolyzed to W2 (n=1, R^2=m-Cl-Bn, R^3=Me) using two equivalent of LiOH in MeOH.

The following compounds were synthesized in similar fashion:

#	Structure	MW	Obs. m/e
1423		295	296

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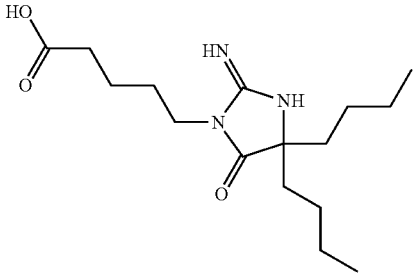
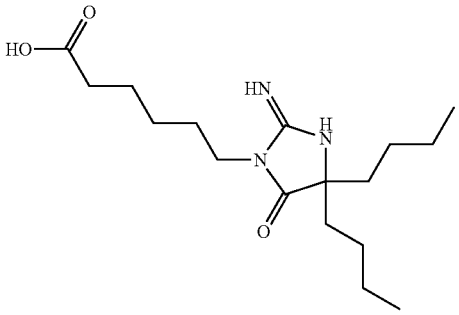
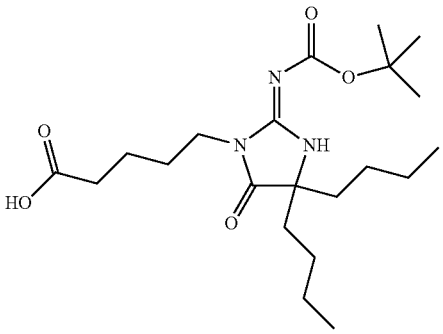
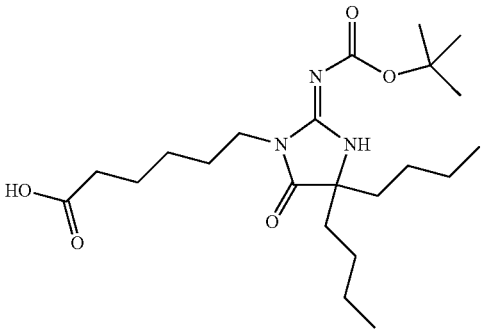
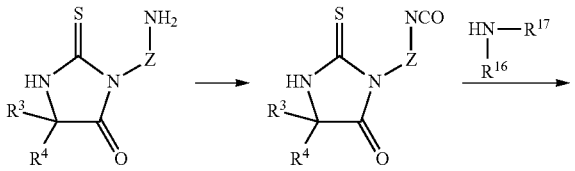
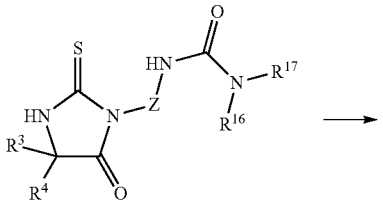
#	Structure	MW	Obs. m/e
1424		311	312
1425		325	326
1426		411	412
1427		425	426

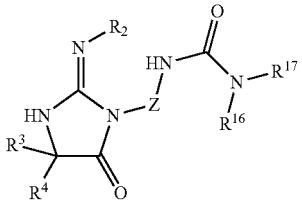
Method X



X1 X2



X3



X4

(In the scheme, —Z—NH—C(O)—N(R^{16})(R^{17})— is equivalent to R^1 substituted by R^{21}, or R^1 Substituted by alkyl-R^{22}, wherein R^{21} and R^{22} are —NH—C(O)—N(R^{16})(R^{17}) and R^{15} is H, and wherein Z is optionally substituted alkylene-arylenen, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method X, Step 1:

To a mixture of the amine X1 obtained using method L (R^3=Me; R^4=^{i}-Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—) (10 mg) in DCM and sat. $NaHCO_3$ (1:1 by volume) was added triphosgene (0.33 eq) at r.t. The solution was stirred vigorously for 40 minutes before the organic layer was separated and dried over anhydrous Na_2SO_4. The organic solution was evaporated to give compound X2 (R^3=Me; R^4=i-Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—).

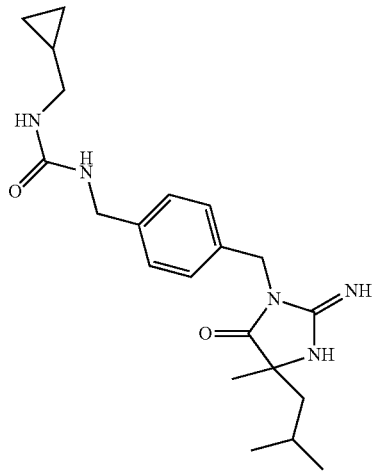
Method X, Step 2:

Compound X3 (R^{15}=H; R^{16}=cyclopropylmethyl; R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—) was prepared from X2 (R^3=Me; R^4=i-Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—) using method similar to method M, step 1.

Method X, Step 3:

Compound X4 (R^{16}=H; R^{17}=cyclopropylmethyl; R^2=H; R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—) was prepared from X3 (R^{16}=H; R^{17}=cyclopropylmethyl; R^2=H; R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—) using method similar to method A Step 3. NMR (CD_3OD): δ 7.25, s, 4H; δ 4.8, m, 2H; δ 4.25, s, 2H; δ 2.9, m, 2H; δ 1.68, m, 2H; δ 1.44, m, 1H; δ 1.36, s, 3H; δ 0.9, m, 1H; δ 0.82, m, 3H; δ 0.66, m, 3H; δ 0.4, m, 2H; δ 0.12, m, 2H. ES_LCMS (m/e) 386.1.

The following compounds were prepared using a similar method.

#	Structure	MW	Obs. m/e
1428		385	386

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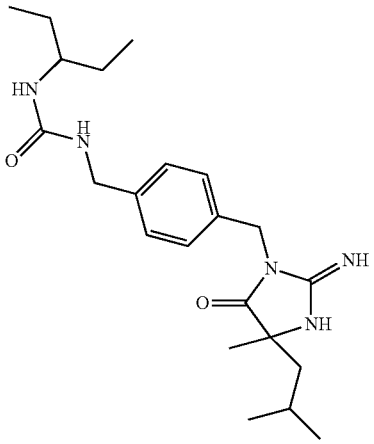
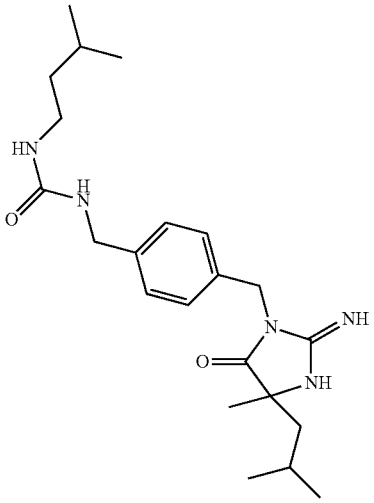
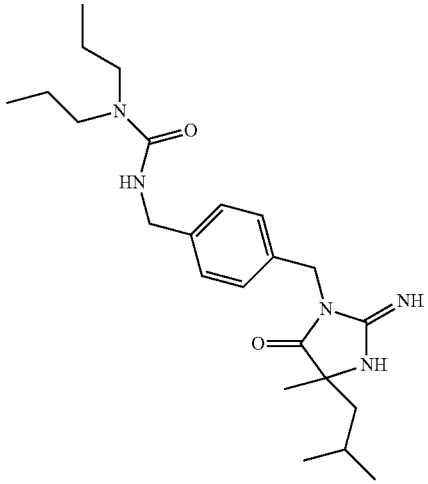
#	Structure	MW	Obs. m/e
1429		401	402
1430		401	402
1431		415	416

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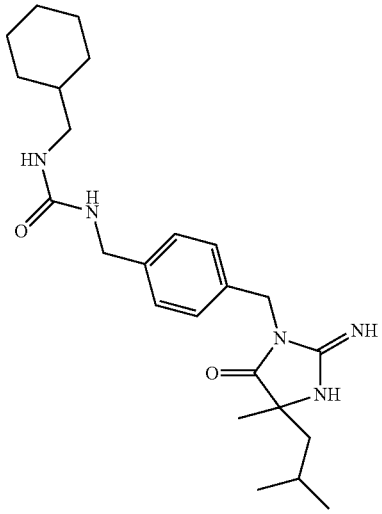
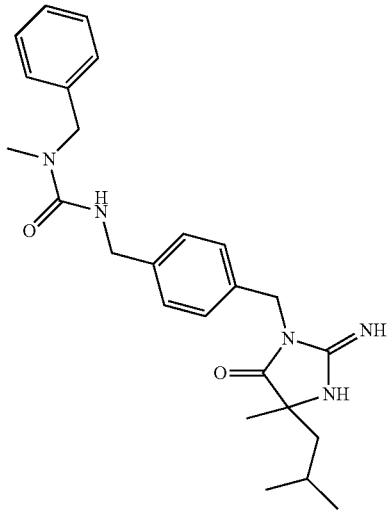
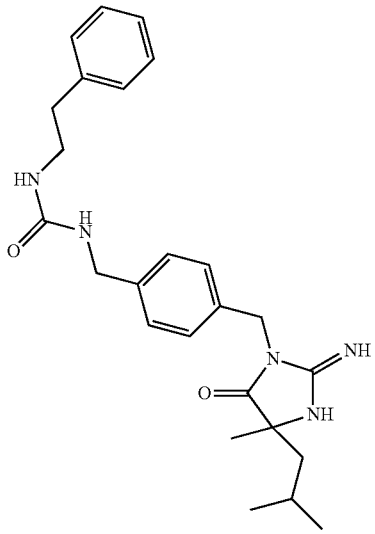
#	Structure	MW	Obs. m/e
1432		427	428
1433		435	436
1434		435	436

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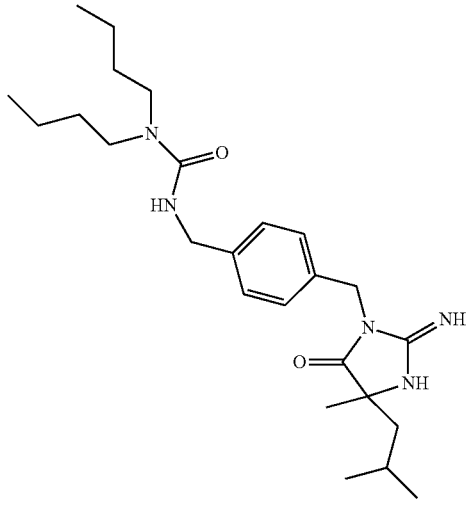
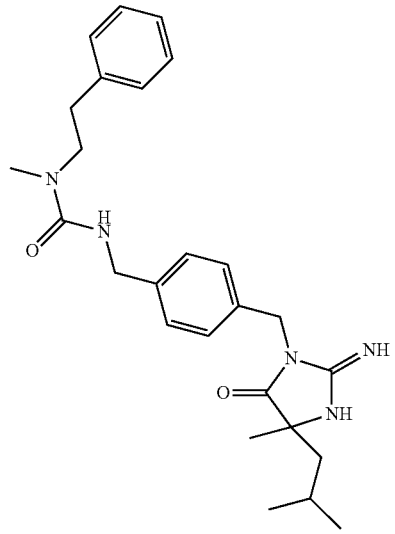
#	Structure	MW	Obs. m/e
1435		443	444
1436		449	450

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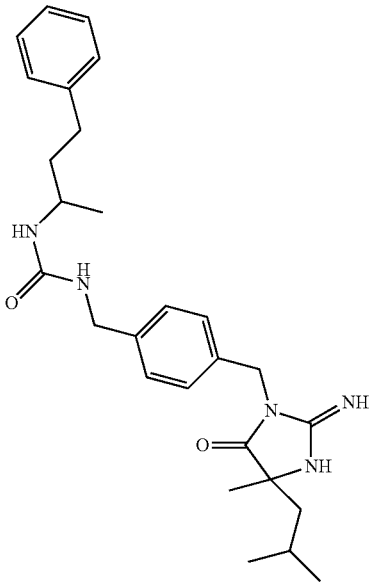
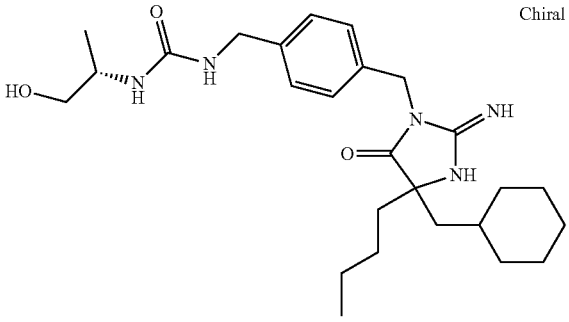
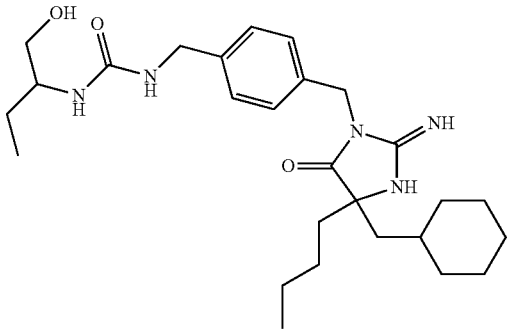
#	Structure	MW	Obs. m/e
1437		463	464
1438		471	472
1439		485	486

Chiral

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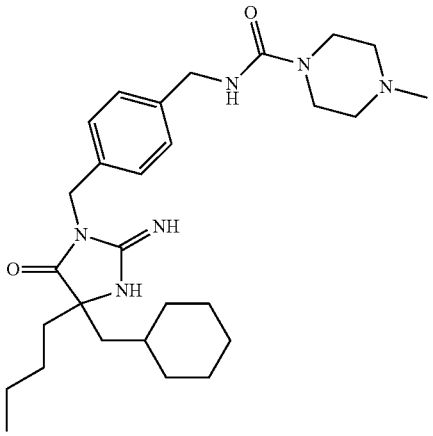
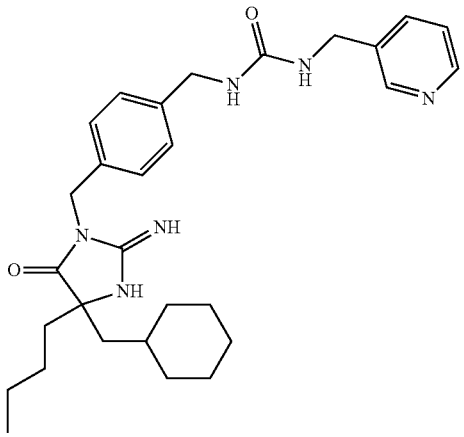
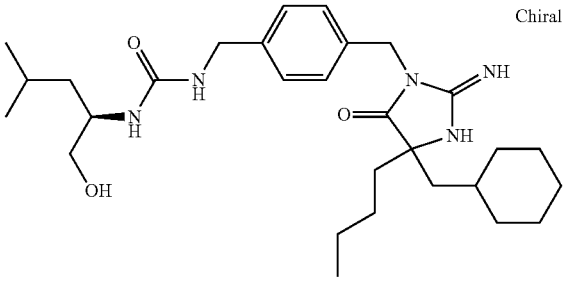
#	Structure	MW	Obs. m/e
1440		496	497
1441		504	505
1442	 Chiral	513	514

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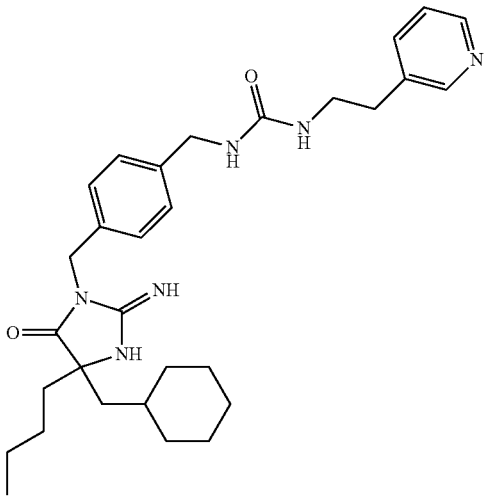
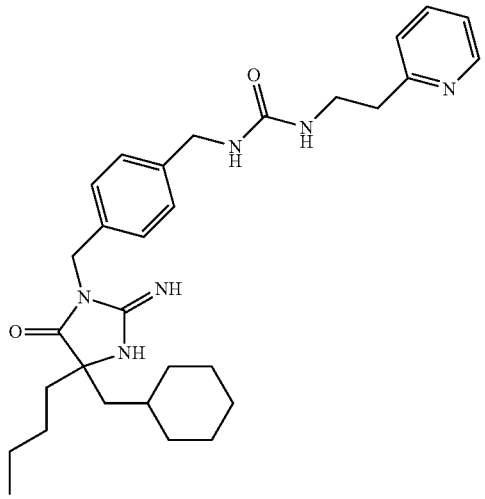
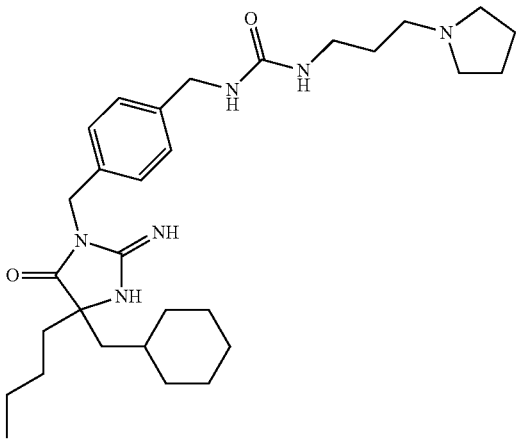
#	Structure	MW	Obs. m/e
1443		518	519
1444		518	519
1445		524	525

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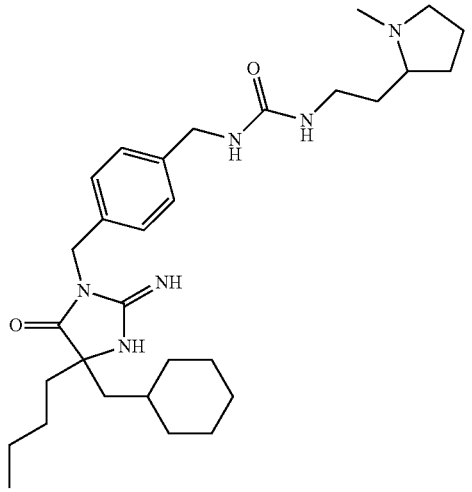
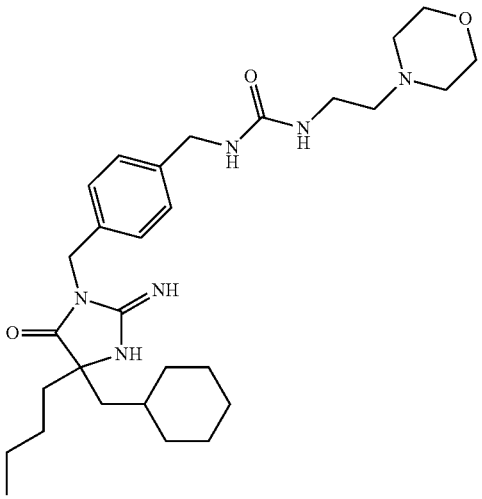
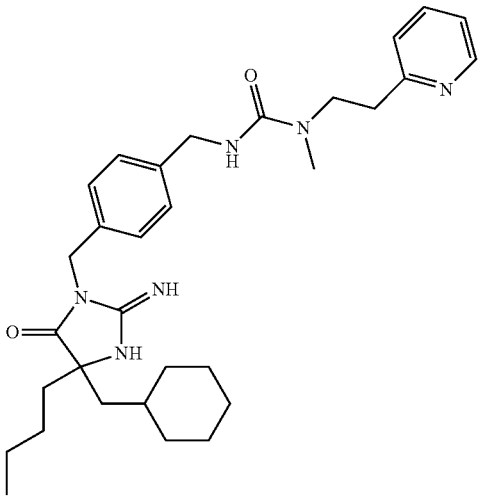
#	Structure	MW	Obs. m/e
1446		524	525
1447		526	527
1448		532	533

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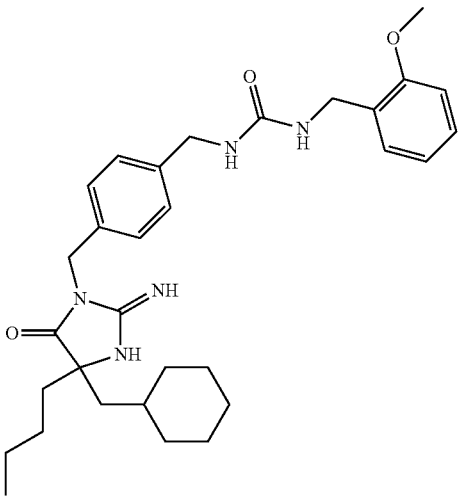
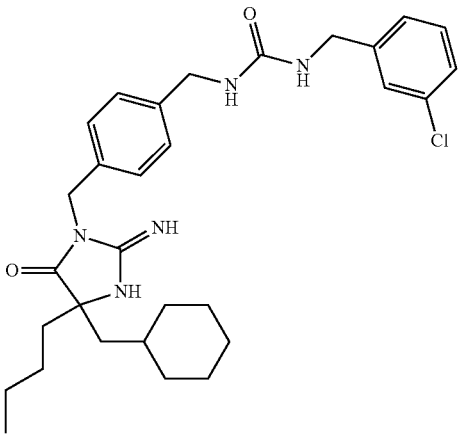
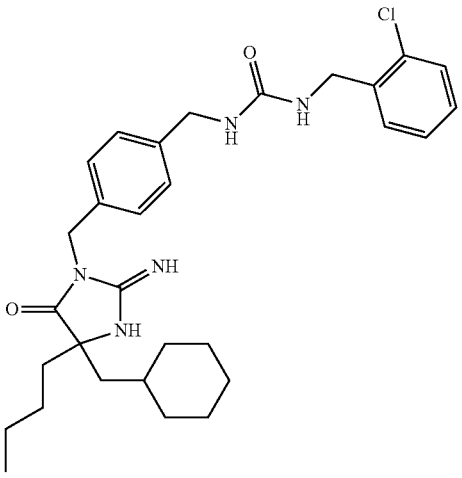
#	Structure	MW	Obs. m/e
1449		533	534
1450		537	538
1451		537	538

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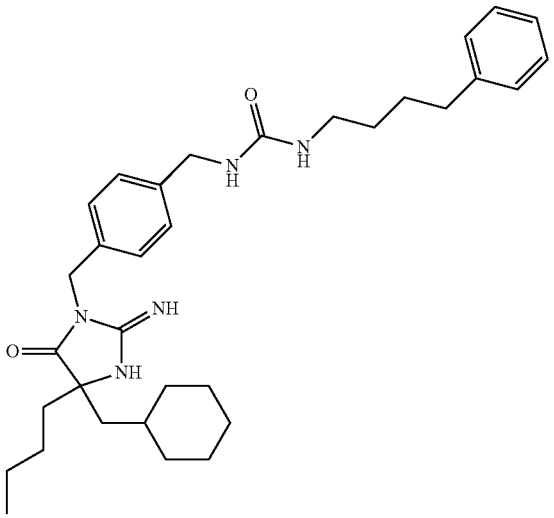
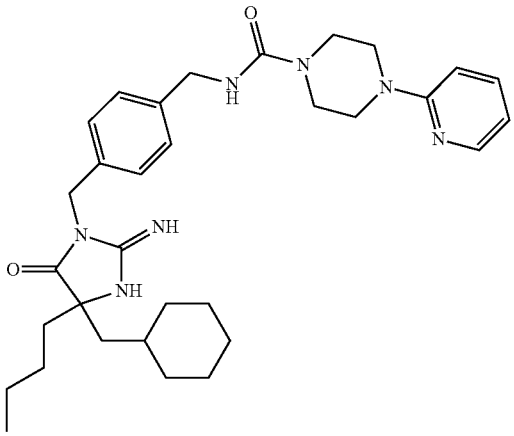
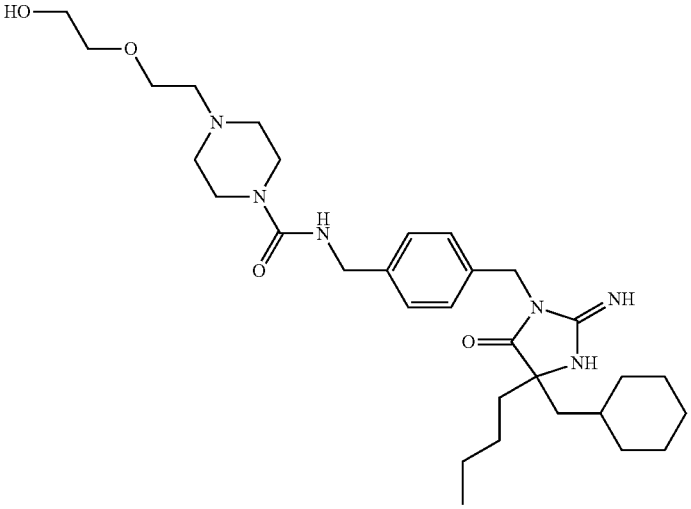
#	Structure	MW	Obs. m/e
1452		545	546
1453		559	560
1454		570	571

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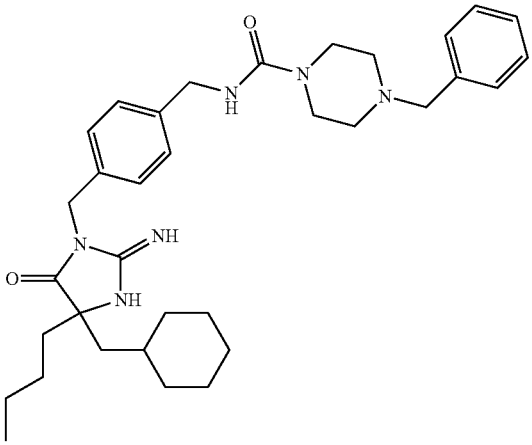
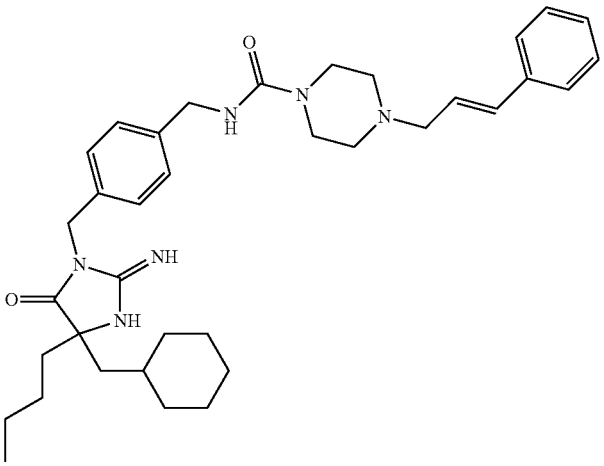
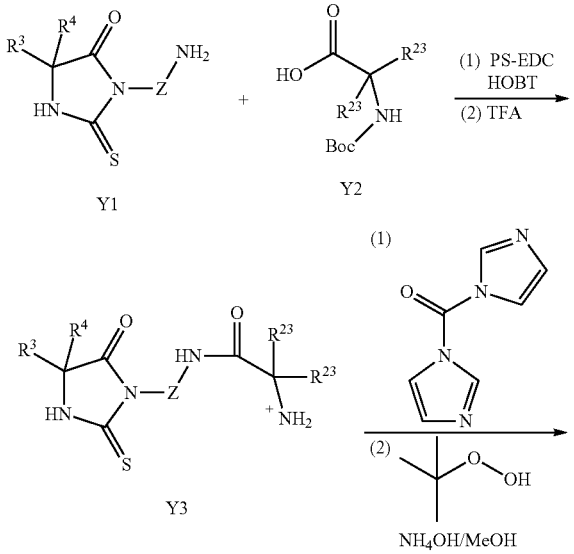
#	Structure	MW	Obs. m/e
1455		572	573
1456		598	599

Method Y



Y1 Y2 Y3

(1) PS-EDC HOBT (2) TFA

(1) (2) NH_4OH/MeOH

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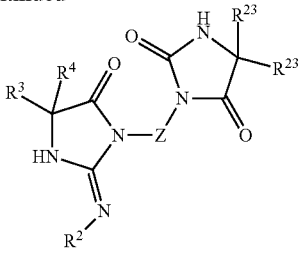
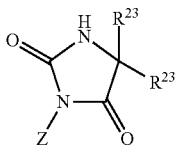


Y4

(In the scheme,



is equivalent to R^1 substituted by R^{21}, or R^1 Substituted by alkyl-R^{22}, wherein R^{21} and R^{22} are —N(R^{15})—C(O)—N

(R^{16})(R^{17}) and R^{15} and R^{16} form a ring as defined above, and wherein Z is optionally substituted alkylene-arylenen, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

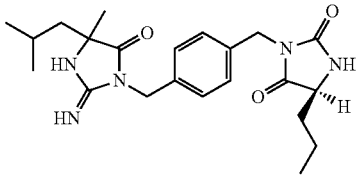
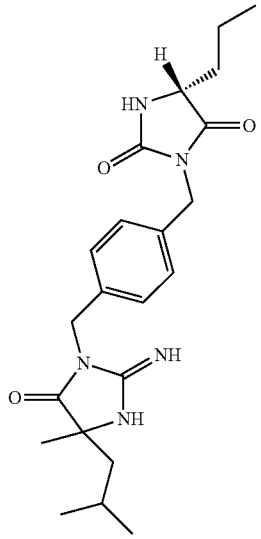
Method Y, Step 1:

The reaction mixture of compound Y1 obtained from Method L (R^3=Me; R^4=i-Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—) (0.1639 mmole), Y2 (R^{23}=H; R^{23}=Pr) (0.1967 mmole), PS-EDC resin (0.4917 mmole) and HOBT (0.2459 mmole) in 3.5 ml of mixture of THF, MeCN and DMF (1:1:0.3) was shaken overnight at RT before 6 eq of PS-trisamine resin 3 eq of PS-isocyanate resin were added. After 6 hrs the reaction mixture was filtered and the resin was washed with THF, DCM and MeOH. The combined filtrate was evaporated and the crude was treated with 40% TFA in DCM for 40 min before the solvent was evaporated and residue purified on RP HPLC system to give product Y3 (R^3=Me; R^4=i-Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—, R^{23}=H; R^{23}=Pr).

Method Y, Step 2:

The reaction solution of Y3 (R^3=Me; R^4=i-Bu; Z=para-$(CH_2)C_6H4CH_2)$—, R^{23}=H; R^{23}=Pr) (0.030 mmole), carbonyl diimidazole (0.032 mmole), and DIEA (0.09 mmole) in 0.5 ml DCM was shaken overweekend at RT. The crude was then purified on reverse column to give the thiohydantoin product which was converted into Y4 (R^2=H; R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—, R^{23}=H; R^{23}=Pr).

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e
1457		413	414
1458		413	414

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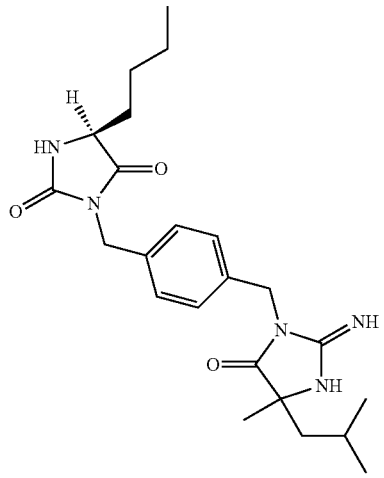
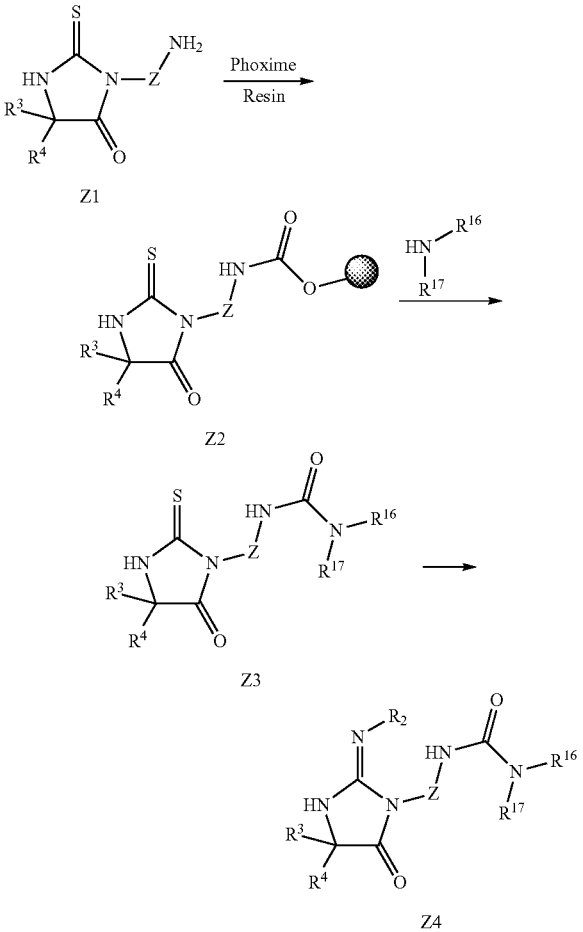
#	Structure	MW	Obs. m/e
1459		427	428

Method Z



(In the scheme, —Z—NH—C(O)—N(R^{16})(R^{17})— is equivalent to R^1 substituted by R^{21}, or R^1 Substituted by

alkyl-R^{22}, wherein R^{21} and R^{22} are —$N(R^{15})$—$C(O)$—$N(R^{16})(R^{17})$ and R^{15} is H, and wherein Z is optionally substituted alkylene-arylenen, alkylene-arylene-alkylene, alkylene-heteroarylene, alkylene-heteroarylene-alkylene, alkylene-cycloalkylene, alkylene-cycloalkylene-alkylene, alkylene-heterocycloalkylene, alkylene-heterocycloalkylene-alkylene, arylene, heteroarylene, cycloalkylene or heterocycloalkylene)

Method Z, Step 1:

To the solution of the Phoxime™ resin (1.23 mmol/g) in DCM was added the amine Z1 obtained from method L (R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—) (2 eq). The mixture was shaken overnight before the resin was filtered and washed with DCM, MeOH, THF (3 cycles), then DCM (×2), dried in vacuum to get resin Z2 (R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—).

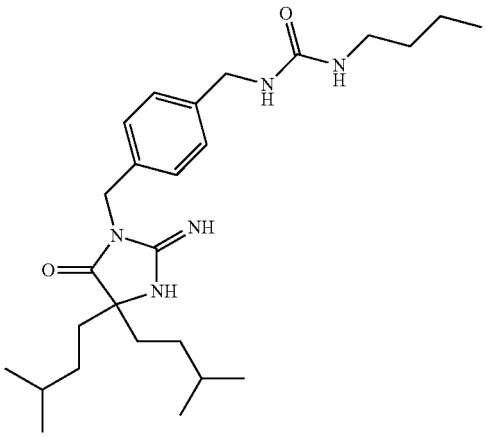
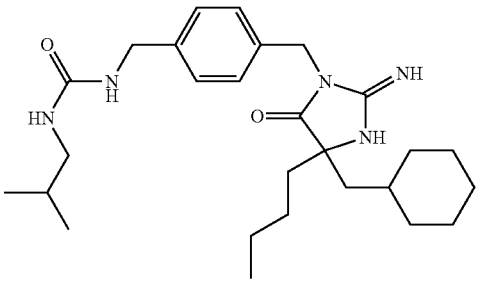
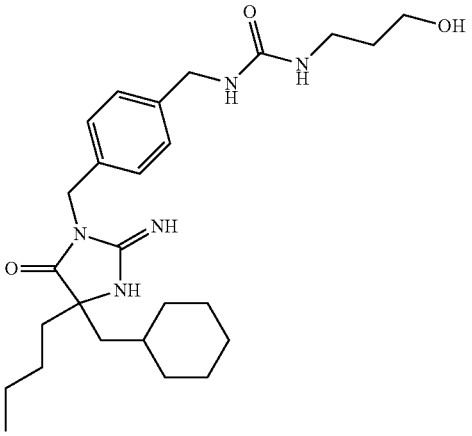
Method Z, Step 2:

To the resin Z2 (R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—), swelled in DCM, in toluene was added N-methylbenzylamine (4 eq). The mixture was heated at 80-90° C. overnight before MP-TSOH resin (1.3 mmol/g, 12 eq) was added. The mixture was shaken for 1.5 hours, the solution was filtered and the resin washed with DCM and MeOH. The combined organic solution was concentrated in vacuo to get Z3 (R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—; R^{16}=Me; R^{17}=Bn).

Method Z, Step 3:

Compound Z4 (R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—; R^{16}=Me; R^{17}=Bn) was generated from Z3 (R^3=Me; R^4=^{i}Bu; Z=para-$(CH_2)C_6H_4(CH_2)$—; R^{16}=Me; R^{17}=Bn) using method similar to Method A step 3.

The following compounds were prepared using similar method.

#	Structure	MW	Obs. m/e
1460		457	458
1461		469	470
1462		471	472

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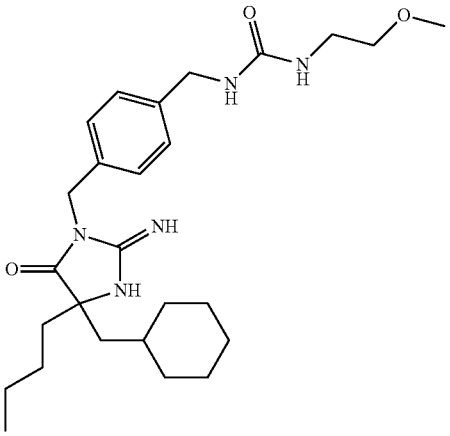
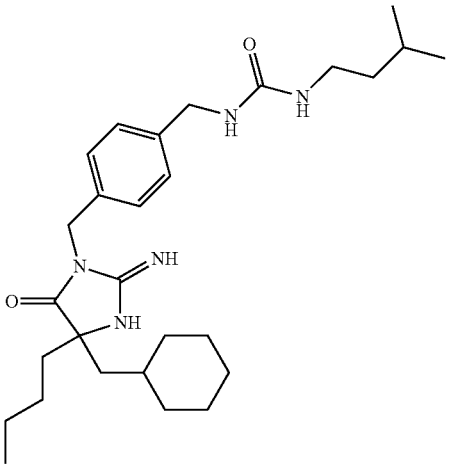
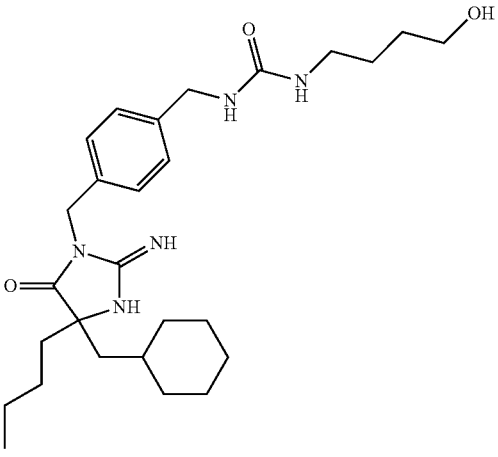
#	Structure	MW	Obs. m/e
1463		471	472
1464		483	484
1465		485	486

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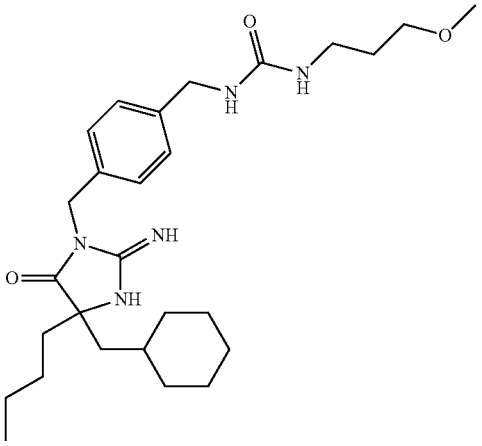
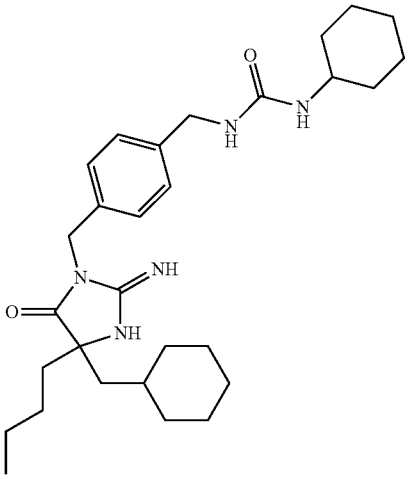
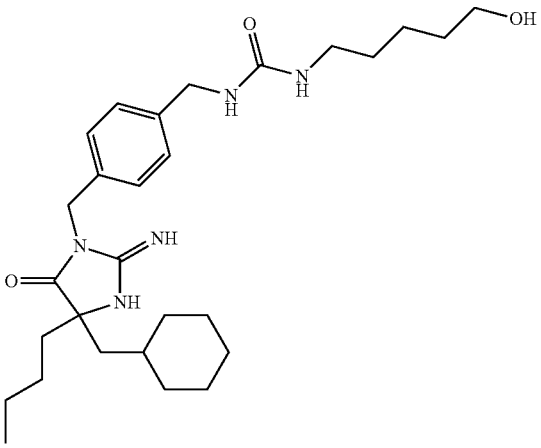
#	Structure	MW	Obs. m/e
1466		485	486
1467		495	496
1468		499	500

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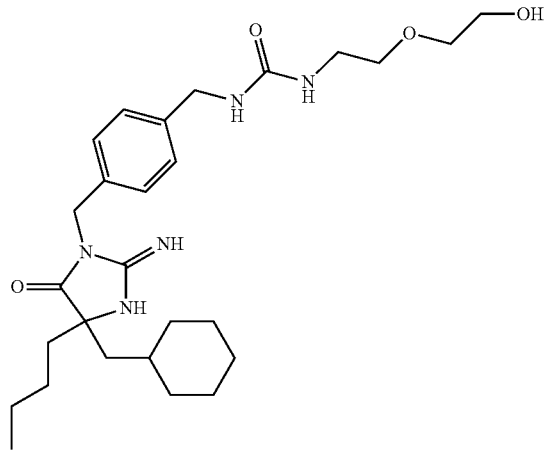
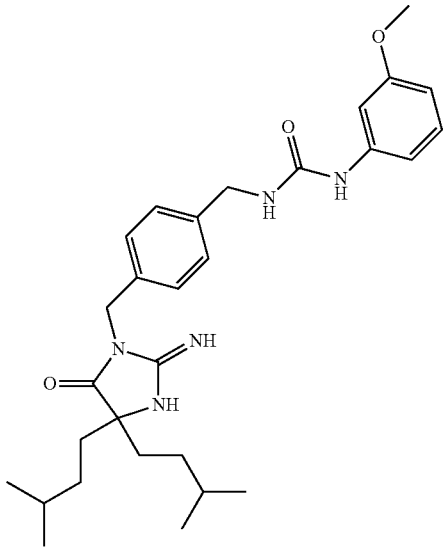
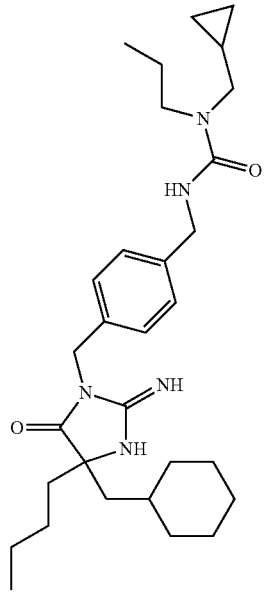
#	Structure	MW	Obs. m/e
1469		501	502
1470		507	508
1471		509	510

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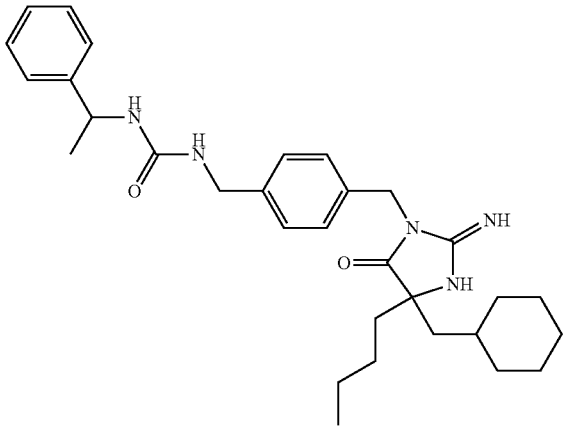
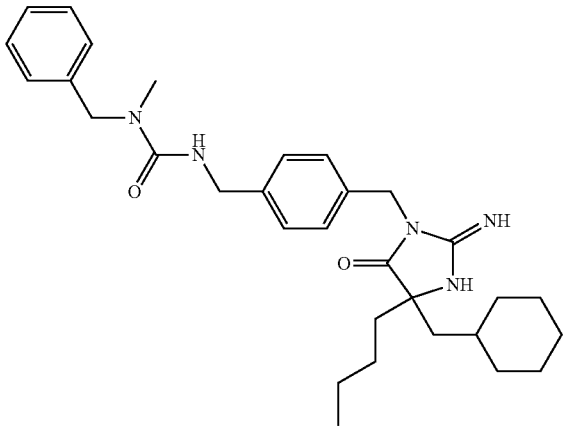
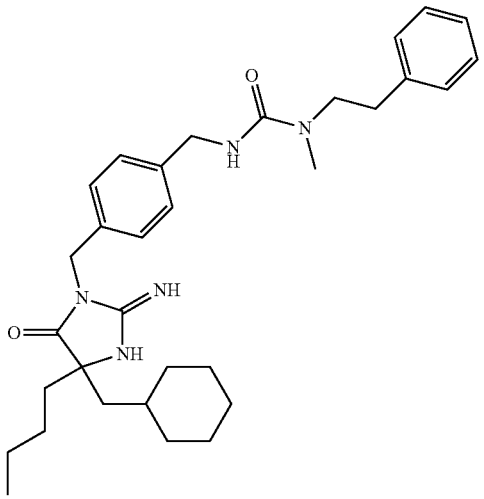
#	Structure	MW	Obs. m/e
1472		517	518
1473		517	518
1474		531	532

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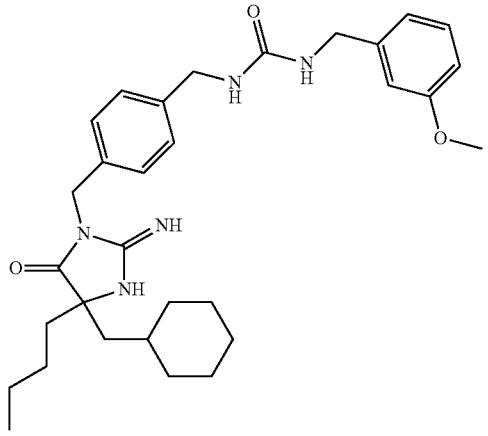
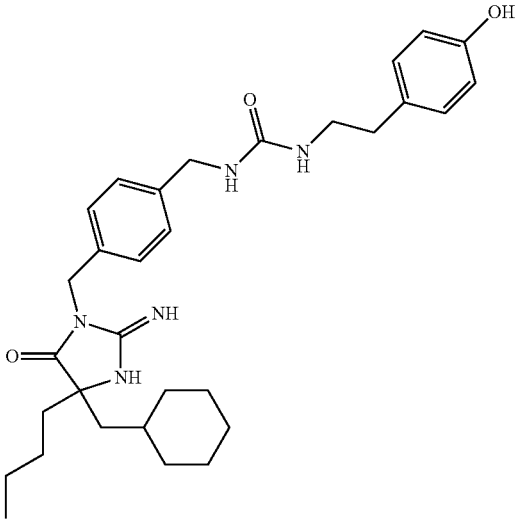
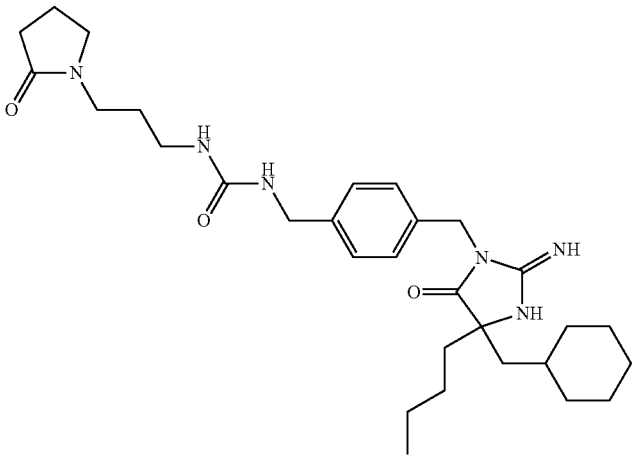
#	Structure	MW	Obs. m/e
1475		533	534
1476		533	534
1477		538	539

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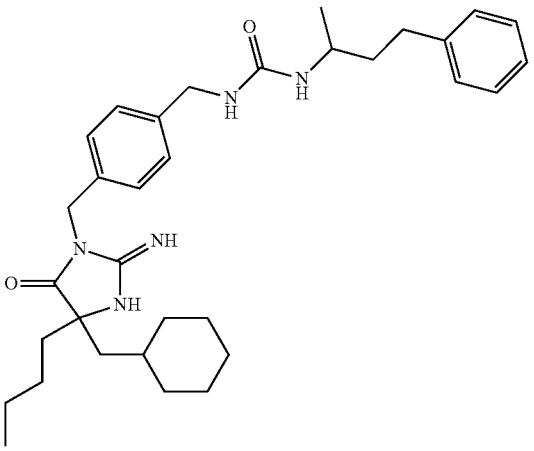
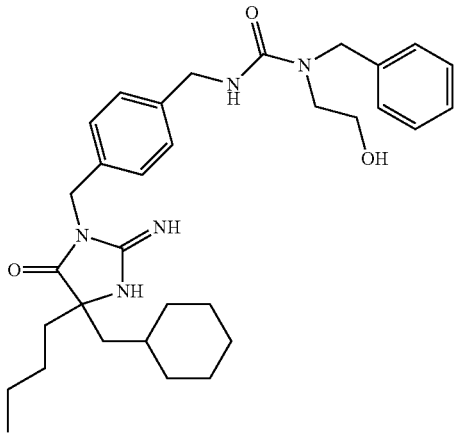
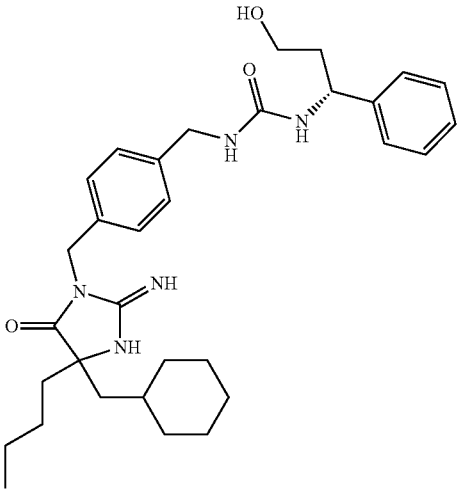
#	Structure	MW	Obs. m/e
1478		545	546
1479		547	548
1480		547	548

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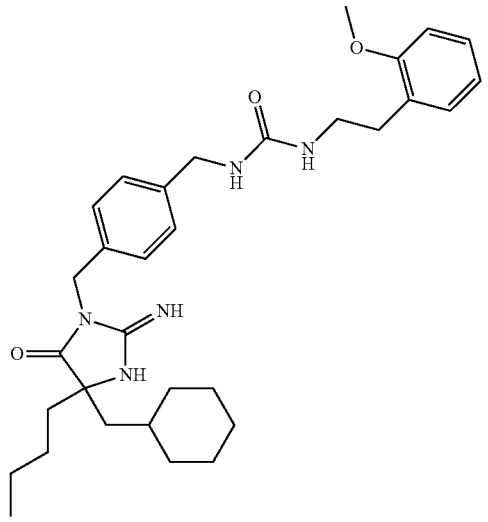
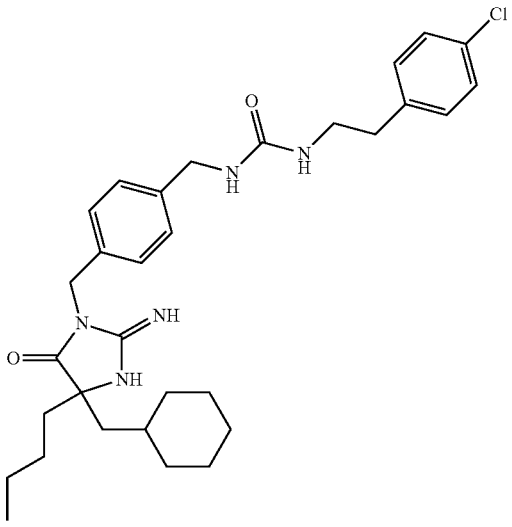
#	Structure	MW	Obs. m/e
1481		547	548
1482		551	552

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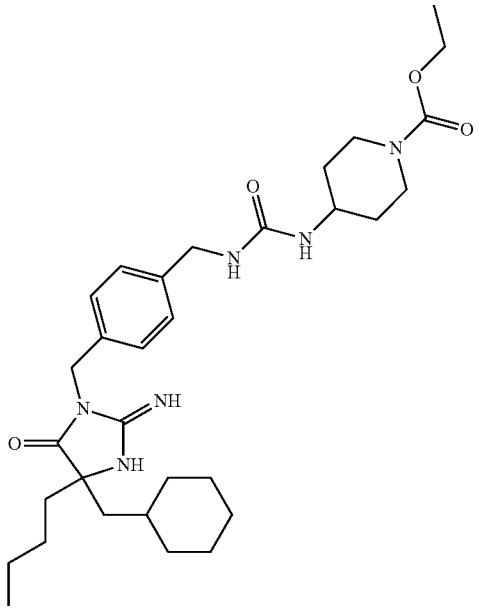
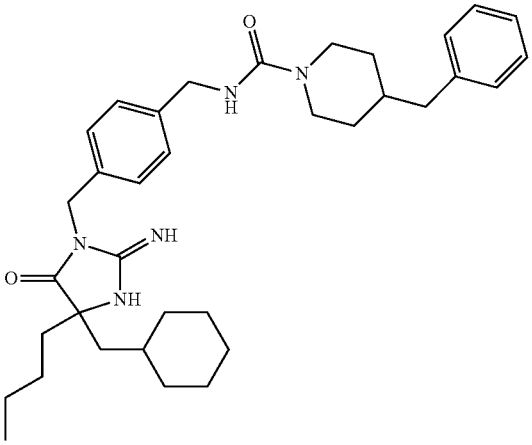
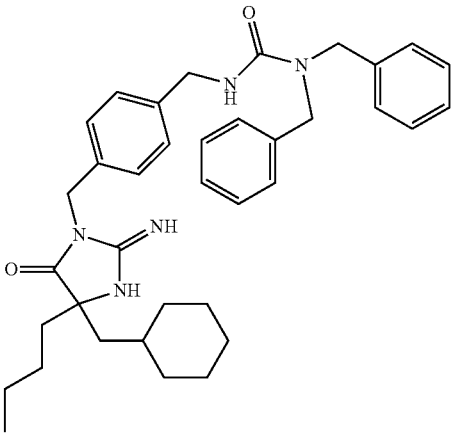
#	Structure	MW	Obs. m/e
1483		568	569
1484		571	572
1485		593	594

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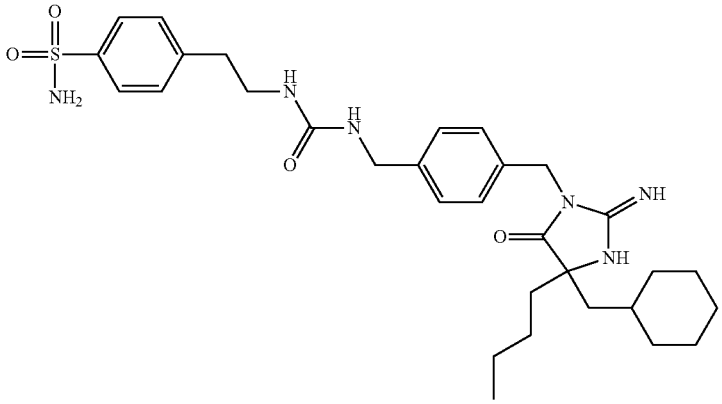
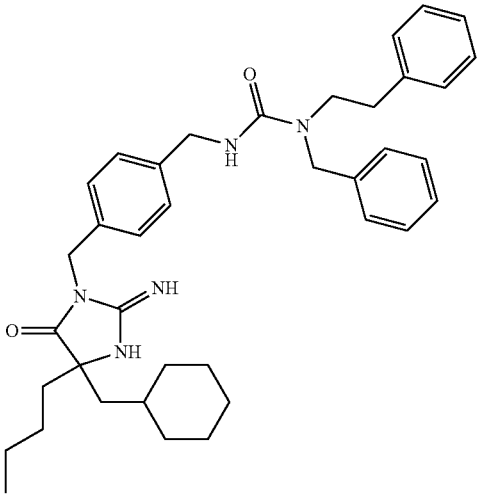
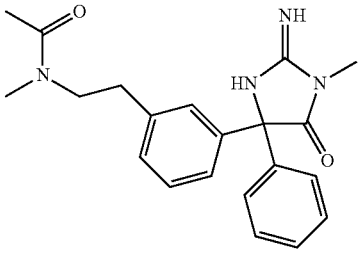
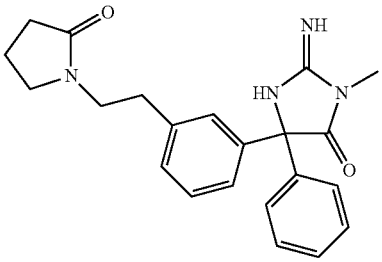
#	Structure	MW	Obs. m/e
1486		596	597
1487		607	608
1488		364	365
1489		377	377

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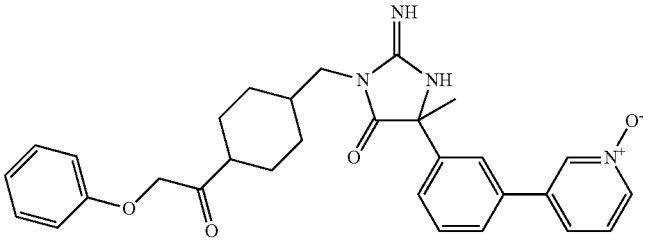
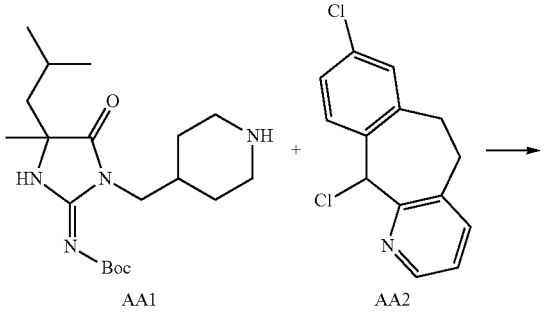
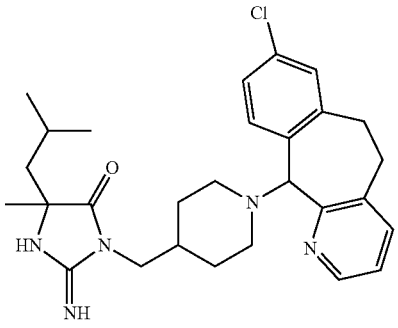
1490		513	514

Method AA

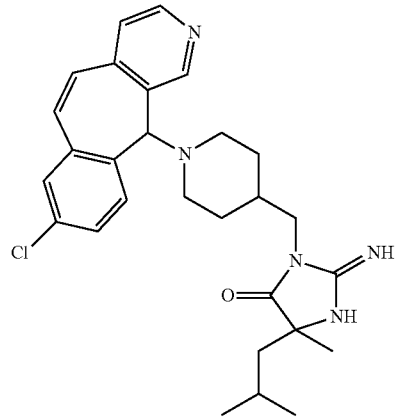
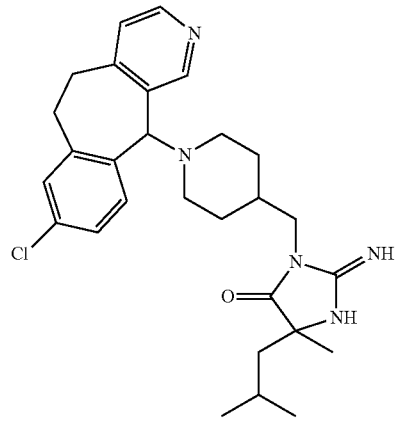


AA1 AA2



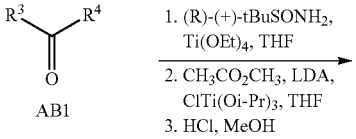
AA3

8,11-Dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (AA2) (18 mg) was reacted with AA1, obtained from method Q, and diisopropylethylamine (14 uL) in acetonitrile (2.5 mL). The resulting mixture was heated at 65° C. for 18 h. The reaction mixture was placed on a preparative silica gel plate and eluted with hexane:ethyl acetate 3:1 to give the desired product which was treated with 40% TFA. Evaporation of the solvent followed by purification afforded compound AA3.

#	Structure	MW	Obs. m/e
187		491	492
188		493	494

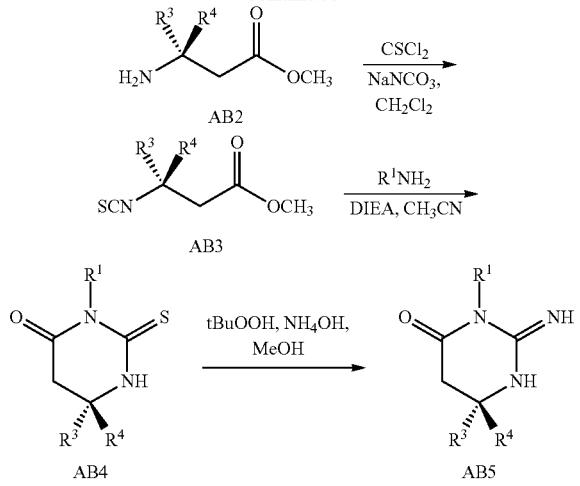
The following compounds were prepared using similar method.

Method AB



AB1

-continued



Method AB, Step 1:

To a solution of (R)-(+)-2-methyl-2-propane sulfonamide (1.0 g, 8.3 mmol, 1 eq) and AB1 (R^3=Ph, R^4=n-Bu) (3 mL, 9.1 mmol, 1.1 eq) in anhydrous THF (30 mL) at room temperature was added $Ti(OEt)_4$ (7 mL, 17 mmol, 2 eq). The mixture was heated at 70° C. for 24 h. After cooling to room temperature, the mixture was poured into 30 mL of brine under vigorous stirring. The resulting suspension was filtered through a pad of Celite and the solid was washed with EtOAc (2× 20 mL). The filtrate was washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica by eluting with hexane/Et_2O (5:1) to give 1.9 g (85%) of (R)-2-methyl-N-(1-phenylpentylidene) propane-2-sulfinamide. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 7.91 (m, 2H), 7.52-7.37 (m, 3H), 3.27 (m, 1H), 3.15 (m, 1H), 1.73-1.61 (m, 2H), 1.47-1.38 (m, 2H), 1.31 (s, 9H), 0.95 (m, 3H). MS(ESI): MH^+=265.9. HPLC t_R=7.24, 7.58 min (E/Z=5.5:1).

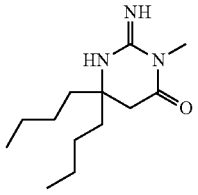
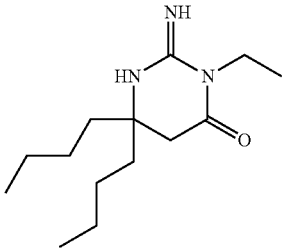
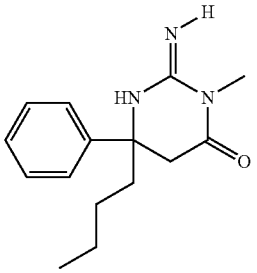
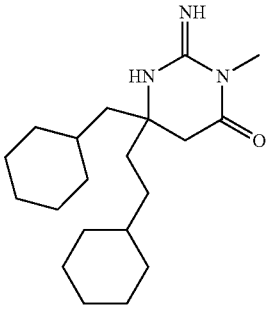
To a solution of methyl acetate (0.6 mL, 6.9 mmol, 2 eq) in THF (5 mL), LDA (2M in heptane/THF, 3.4 mL, 6.9 mmol, 2 eq) was added dropwise via a syringe at −78° C. After stirring at −78° C. for 30 min, a solution of ClTi(Oi-Pr)$_3$ (1.8 mL, 7.6 mmol, 2.2 eq) in THF (5 mL) was added dropwise. After stirring for another 30 min, a solution of (R)-2-methyl-N-(1-phenylpentylidene)propane-2-sulfinamide (0.9 g, 3.4 mmol, 1 eq) in THF (2 mL) was added dropwise via a syringe. The mixture was stirred at −78° C. for 3 h and TLC showed no starting material left. A saturated aqueous solution of NH_4Cl (10 eq) was added and the suspension was warmed to room temperature. The mixture was diluted with H_2O (50 mL) and stirred for 10 min. The mixture was then partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3× 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give 1.1 g of a brown oil. Chromatography on silica gel using 50% EtOAc/hexanes as eluent gave 0.8 g (76%) of methyl 3-((R)-2-methylpropan-2-ylsulfinamido)-3-phenylheptanoate as a yellow oil. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 7.15-7.07 (m, 5H), 3.35 (s, 1H), 3.19 (dd, J=16, 5.6 Hz, 1H), 3.01 (dd, J=15.8, 5.5 Hz, 1H), 2.07 (m, 2H), 1.71 (m, 2H), 1.35-1.26 (m, 4H), 1.17 (s, 9H), 0.89 (m, 3H). MS(ESI): MH^+=339.9. HPLC t_R=7.50, 7.6 min (E/Z=1.5:1)

To a solution of methyl 3-((R)-2-methylpropan-2-ylsulfinamido)-3-phenylheptanoate (0.4 g, 1.1 mmol) in 12 mL of MeOH was added 16 mL of 4N HCl/dioxane. After stirring for 30 min, the volatiles were removed in vacuo. The residue was re-dissolved in MeOH (6 mL), stirred for 5 min, and evaporated again to afford 0.30 g (97%) of AB2 (R^3=Ph, R^4=n-Bu) as a yellow solid. ^{1}HNMR ($CDCl_3$, 300 MHz): δ 9.01 (br s, 2H), 7.37-7.12 (m, 5H), 3.64 (m, 1H), 3.54 (s, 3H), 3.31 (m, 1H), 2.09 (m, 2H), 1.8 (m, 2H), 1.1 (m, 4H), 1.07 (s, 9H), 0.7 (m, 3H). MS(ESI): MH^+=235.9. HPLC t_R=4.72 min.

Method AB, Step 2:

Treatment of compound AB2 (R^3=Ph, R^4=n-butyl) with thiophosgene in CH_2Cl_2 in the presence of aqueous $NaHCO_3$ at 0° C. generates isothiocyanate AB3 (R^3=Ph, R^4=n-butyl) which was converted into final product using method similar to Method A Step 2 and Method A Step 3 to give product AB5 (R^3=Ph, R^4=n-butyl, R^1=Me). ^{1}HNMR ($CDCl_3$, 300 MHz): δ 10.4 (br s, 1H), 7.25-7.11 (m, 5H), 3.23 (dd, J=16, 5.6 Hz, 1H), 3.03 (s, 3H), 2.8 (dd, J=15.8, 5.5 Hz, 1H), 2.49 (s, 1H), 1.78 (m, 2H), 1.1-1.0 (m, 4H), 0.99 (m, 3H). MS(ESI): MH^+=260.2. HPLC t_R=5.09 min.

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e
189		239	240
190		253	254
191		259	260
192		333	334

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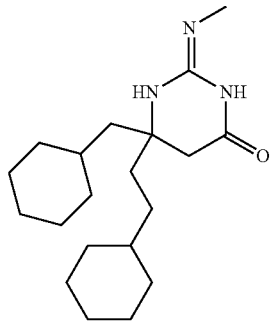
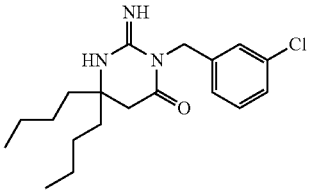
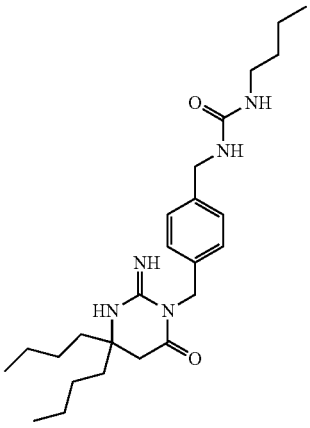
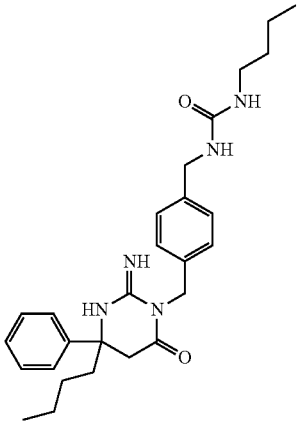
193		333	334
194		349	350
195		443	444
196		463	464

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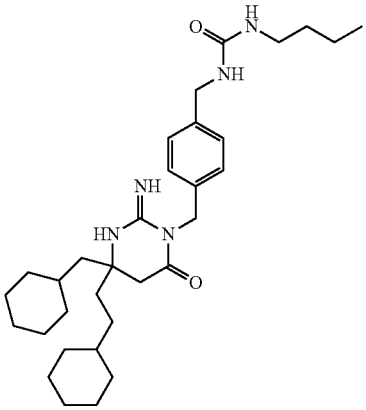
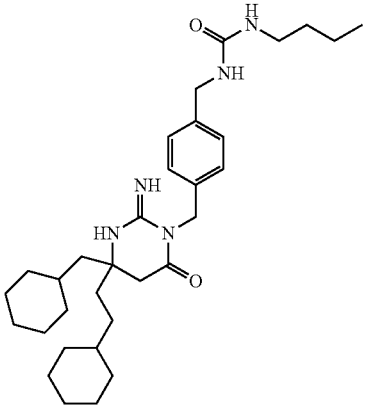
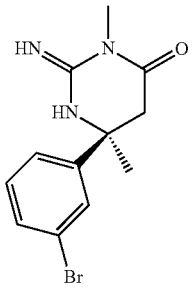
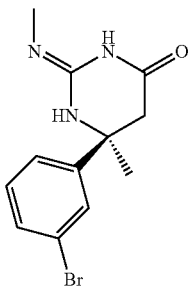
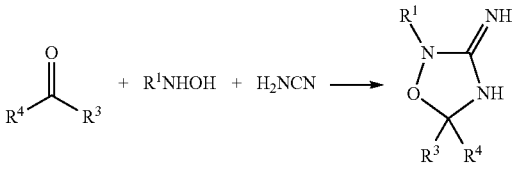
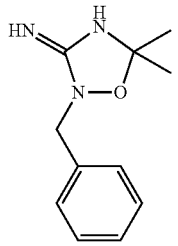
197		537	538
198		537	538
199		295	296
200		295	296

Method AC

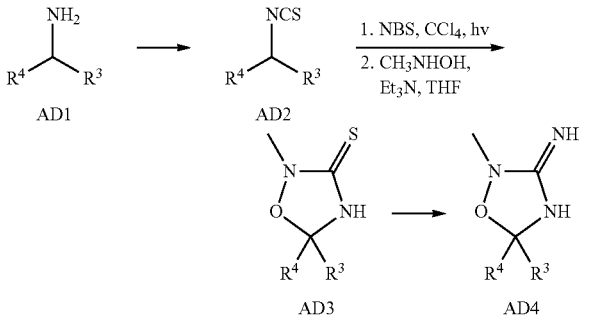


AC1 AC2 AC3

The synthesis was adapted from a procedure by Hull, R. et al, *J. Chem. Soc.* 1963, 6028-6033. Thus, to a solution of AC2 (R^1=Benzyl) (0.72 g, 5.9 mmol) in AC1 (R^4=Me, R^3=Me) (1.4 mL) was added a 50% aqueous solution of cyanamide (0.31 mL, 8.0 mmol). The reaction was heated with stirring at reflux (~40° C.) for 0.5 h, then cooled to 25° C. and stirred for an additional 16 h. The volatiles were removed in vacuo and the residue was partitioned between ether and H_2O. The organic layer was dried over Na_2SO_4, filtered and the volatiles were removed in vacuo. The residue was purified by column chromatography using 5-10% CH_3OH/CH_2Cl_2 as eluent followed by reverse phase preparative HPLC to give 0.15 g (8.0%) of AC3 (R^1=benzyl, R^4=Me and R^3=Me) as a white solid. ^{1}H NMR (CH_3OH, 300 MHz): δ 7.35-7.33 (m, 5H), 4.71 (s, 2H), 1.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.8, 135.6, 129.1, 128.5, 127.9, 104.2, 59.6, 28.8. MS (ESI) m/e 206.1 $(M+H)^+$.

#	Structure	MW	Obs. m/e
201		205	206

Method AD



AD1 AD2 AD3 AD4

Method AD, Step 1:

AD2 (R^3=Ph, R^4=^{1}Butyl) was prepared from AD1 using method similar to Method AB, step 2.

Method AD, Step 2:

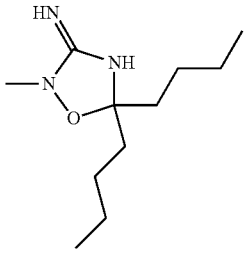
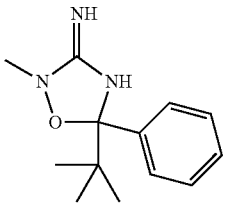
The synthesis was adapted from a procedure by Hussein, A. Q. et al, *Chem. Ber.* 1979, 112, 1948-1955. Thus, to a mixture of AD2 (R^3=Ph, R^4=tert-Butyl) (0.56 g, 2.7 mmol) and boiling chips in CCl_4 (25 mL) was added N-bromosuccinimide (0.49 g, 2.7 mmol). The mixture was irradiated with a 200 watt light source for 1 h. The reaction was cooled, the solid filtered off and the volatiles were removed in vacuo. Chromatography on silica gel by eluting with 5% EtOAc/hexane gave 0.57 g (73%) of 1-(1-bromo-1-isothiocyanato-2,2-dimethylpropyl)benzene as a beige powder. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63-7.61 (m, 2H), 7.37-7.26 (m, 3H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.1, 129.0, 128.9, 128.6, 127.5, 91.2, 45.6, 26.6. MS (ESI) m/e 284.9 $(M+H)^+$.

To a solution of 1-(1-bromo-1-isothiocyanato-2,2-dimethylpropyl)benzene (0.13 g, 0.47 mmol) and the hydrochloride salt of N-methylhydroxylamine (0.047 g, 0.57 mmol) in THF (3 mL) was added triethylamine (0.18 mL, 1.32 mmol). The mixture was stirred at 25° C. for 16 h, filtered and the volatiles were removed in vacuo. The residue was purified by column chromatography using CH_3OH/CH_2Cl_2 as eluent to give 0.050 g (42%) of AD3 (R^3=Ph, R^4=tert-Butyl) as a glassy solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.26 (m, 5H), 3.38 (s, 3H), 1.0 (s, 9H); MS (ESI) m/e 251.1 $(M+H)^+$.

Method AD, Step 2:

To a solution of AD3 (R^3=Ph, R^4=tert-Butyl) (0.065 g, 0.26 mmol) in CH_3OH (5 mL) at 0° C. was added a solution of aqueous ammonia (2 mL) followed by a 70% aqueous solution of t-butylhydroperoxide (2 mL). The reaction was allowed to warm to 25° C. and stirred for 16 h, The volatiles were removed and the residue was purified by reverse phase HPLC to give 2.0 mg (2.2%) of AD4 (R^3=Ph, R^4=tert-Butyl) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47-7.43 (m, 2H), 7.39-7.35 (m, 3H), 3.23 (s, 3H), 1.0 (s, 9H); MS (ESI) mile 234.2 $(M+H)^+$.

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e
202		213	214
203		233	234

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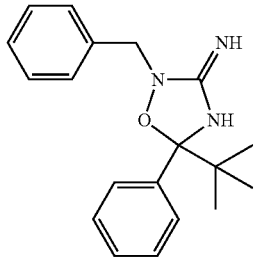
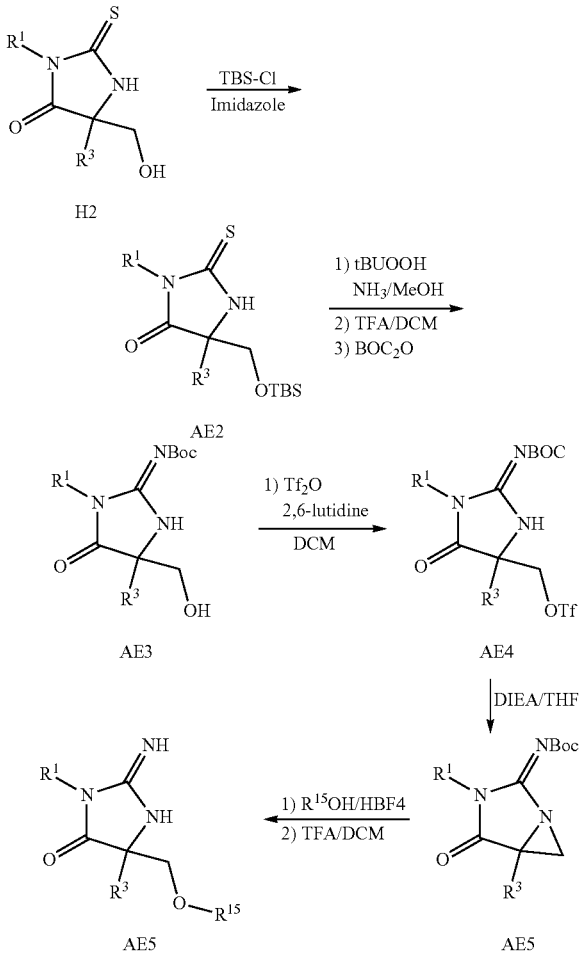
204		309	310

Method AE



Method AE, Step 1:

TBDMS-Cl (5.3 g, 35.19 mmole) and imidazole (2.4 g, 35.19 mmole) were added to a suspension of H2 (R^1=Me, R^3=cyclohexylmethyl) (8.2 g, 31.99 mmole) in 220 ml DCM. The reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered, and the filtrate was diluted with 1200 ml EtOAc. The organic phase was washed with saturated $NaHCO_3$ 3× and brine 3×, and dried over anhydrous Na_2SO_4 to give 12 g of AE2 (R^1=Me, R^3=cyclohexylmethyl), which was used for next step without further purification.

Method AE, Step 2:

AE2 (R^1=Me, R^3=cyclohexylmethyl; 12 grams crude) was converted to iminohydantoin using conditions similar to Method A Step 3, which was subsequently treated with 75% TFA in DCM at room temperature for 24 hrs. The solvent was evaporated in vacuo to give 13.6 g of a product that was reacted with Boc anhydride to give 5.8 g AE3 (R^1=Me, R^3=cyclohexylmethyl) after column purification.

Method AE, Step 3:

AE4 (R^1=Me, R^3=cyclohexylmethyl)(8.2 g) was obtained from AE3 (5.8 g) according to the step 4 of the method H.

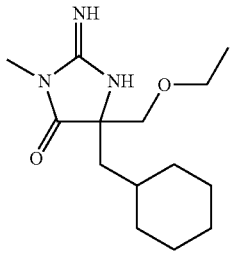
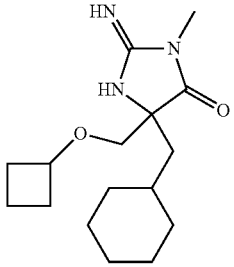
Method AE, Step 4:

To a solution of AE4 (R^1=Me, R^3=cyclohexylmethyl) ((3.95 g, 8.38 mmol) in anhydrous THF (98 mL) was added diisopropylethylamine (7 mL, 40 mmol). The reaction was stirred under N_2 (gas) at room temperature. After 5.5 h, the reaction was concentrated and the crude material was purified via flash chromatography eluting with a gradient of 0 to 75% ethyl acetate in hexane to afford AE5 (R^1=Me, R^3=cyclohexylmethyl) (2.48 g, 92%).

Method AE, Step 4:

To a solution of $R^{15}OH$ (R^{15}=cyclobutyl) (10 μl) and HBF_4 (1 equiv) in anhydrous methylene chloride (0.5 mL) was added a solution of AE5 (R^1=Me, R^3=cyclohexylmethyl) (20 mg, 0.062 mmol) in methylene chloride (0.5 mL). The reaction was agitated overnight at rt. Trifluoroacetic acid (1 mL) was added to the reaction mixture and the solution was agitated for 1 h at rt. The reaction was concentrated and the crude material was purified via reverse phase preparative HPLC/MS eluting with a 7 min gradient of 5 to 95% CH_3CN in H_2O with 0.1% formic acid to afford AE5 (R^1=Me, R^3=cyclohexylmethyl, R^{15}=cyclobutyl).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e
205		267	268
206		293	294

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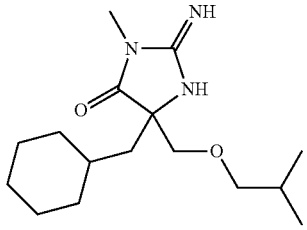
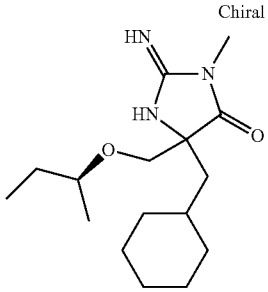
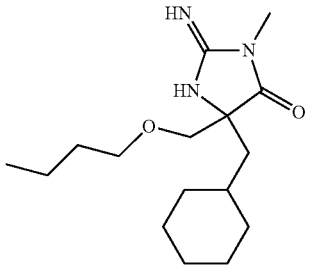
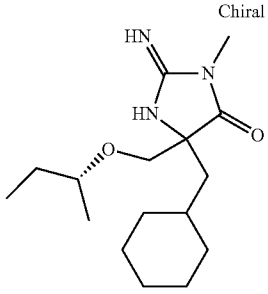
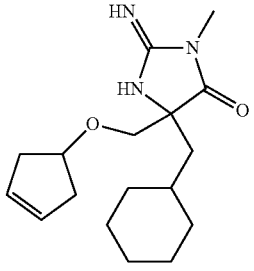
#	Structure	MW	Obs. m/e
207		295	296
208	Chiral 	295	296
209		295	296
210	Chiral 	295	296
211		305	306

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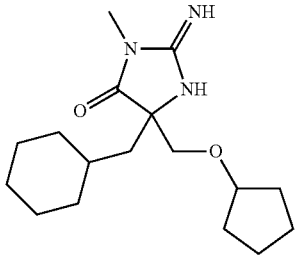
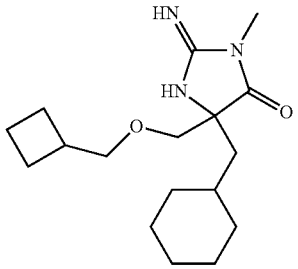
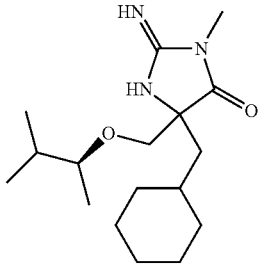
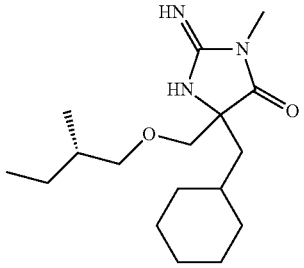
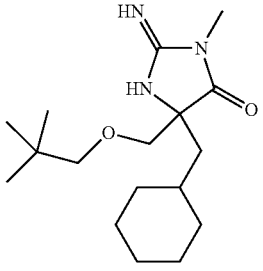
#	Structure	MW	Obs. m/e
212		307	308
213		307	308
214	Chiral 	309	310
215	Chiral 	309	310
216		309	310

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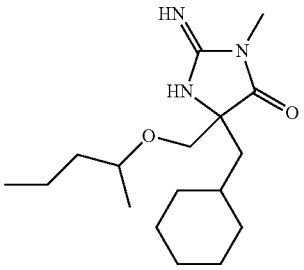
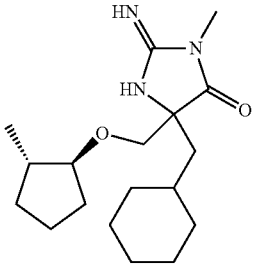
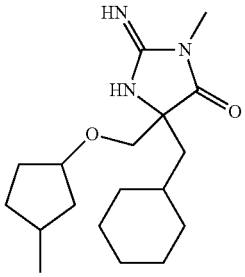
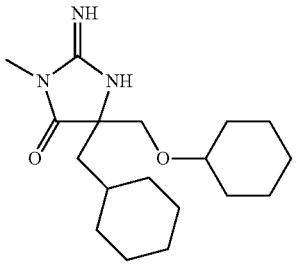
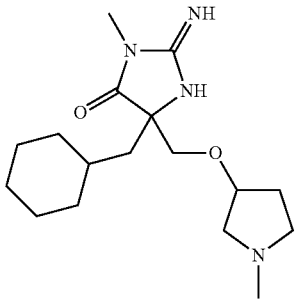
#	Structure	MW	Obs. m/e
217		309	310
218		321	322
219		321	322
220		321	322
221		322	323

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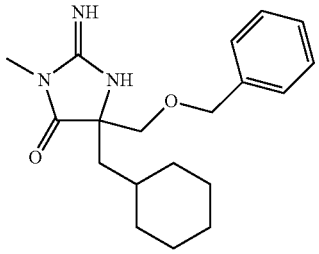
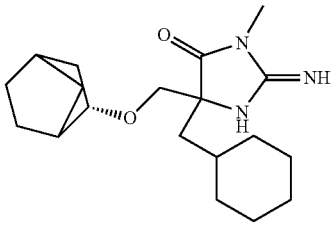
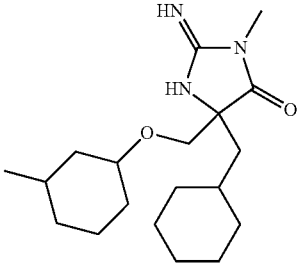
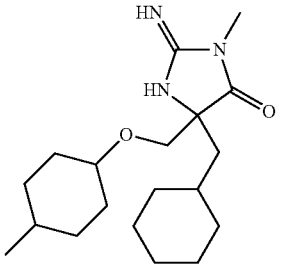
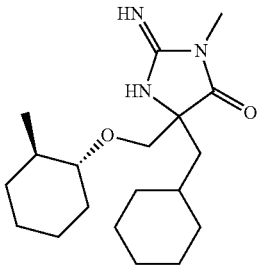
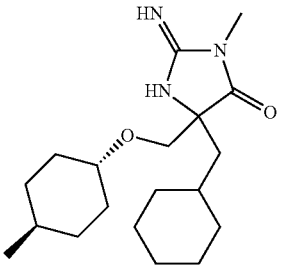
222		329	330
223		333	334
224		335	336
225		335	336
226		335	336
227		335	336

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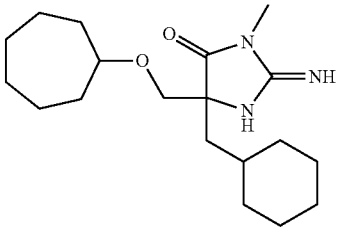
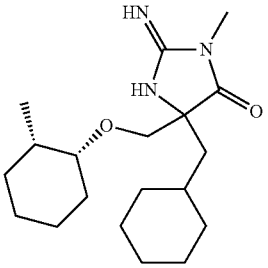
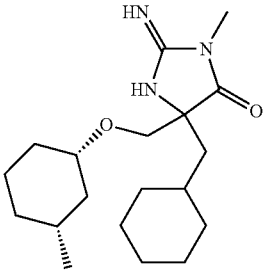
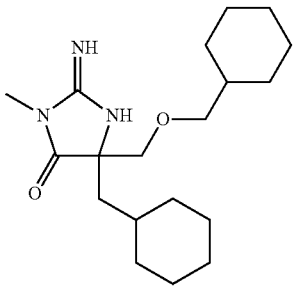
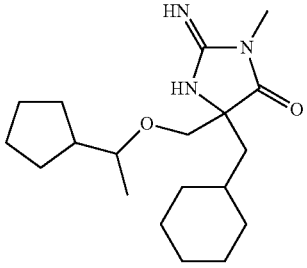
#	Structure	MW	Obs. m/e
228		335	336
229		335	336
230		335	336
231		335	336
232		335	336

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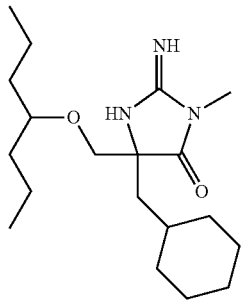
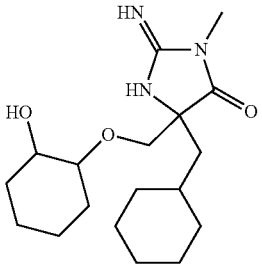
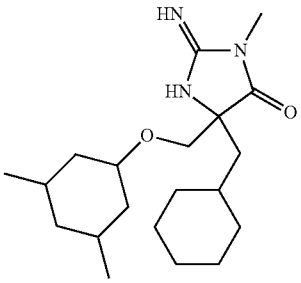
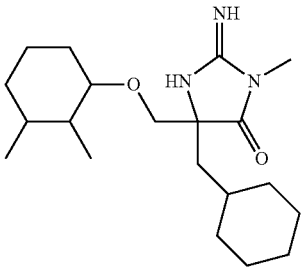
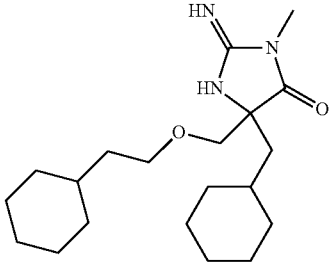
#	Structure	MW	Obs. m/e
233		337	338
234		337	338
235		349	350
236		349	350
237		349	350

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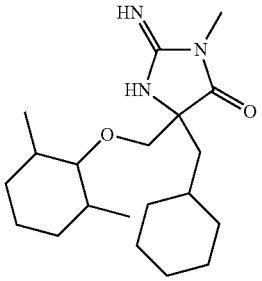
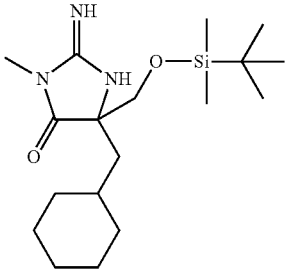
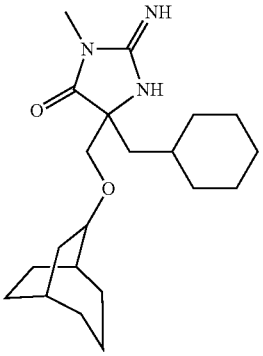
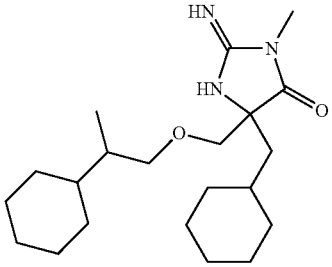
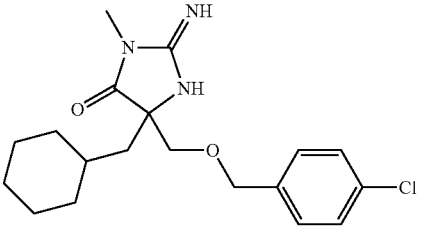
#	Structure	MW	Obs. m/e
238		349	350
239		353	354
240		361	362
241		363	364
242		363	364

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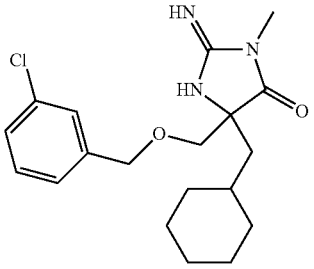
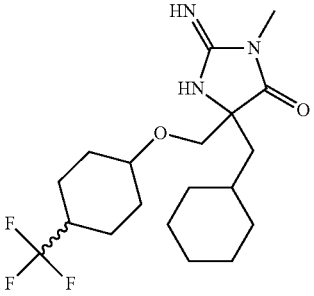
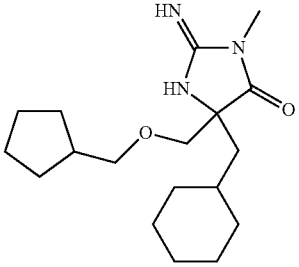
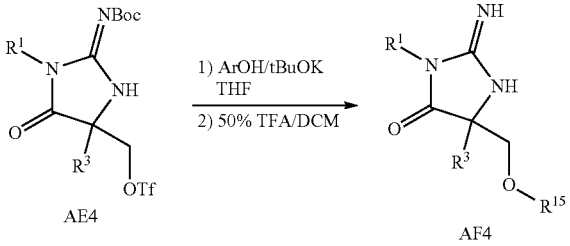
243		363	364
244		389	390
245		321	NA

Method AF

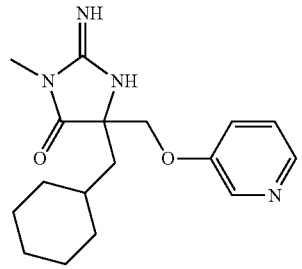
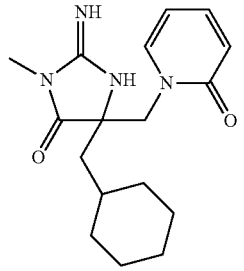
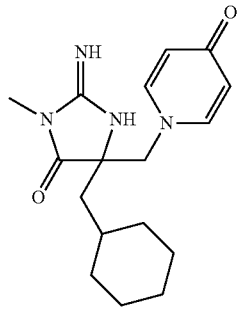
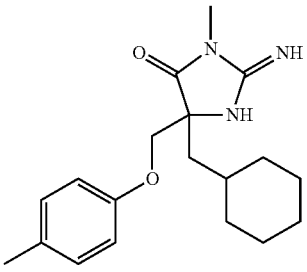
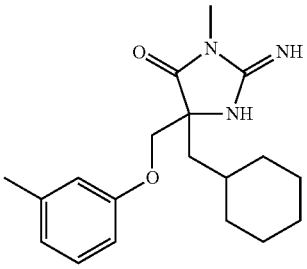


AE4 AF4

To a solution of tBuOK (9.5 mg, 0.0848 mmole) in 0.5 ml anhydrous THF was added ArOH (Ar=m-Chlorophenyl)(13 μl, 0.1273 mmole) in 0.5 ml anhydrous THF followed by addition of AE4 (R^1=Me, R^3=cyclohexylmethyl) (20 mg, 0.0424 mmole) in 0.5 ml anhydrous THF. The reaction mixture was stirred at room temperature for 2 days before it was diluted with 1 ml MeCN, treated with 100 mg MP-TsOH resin and 100 mg Amberlyst A26 resin. The resin was removed by filtration and the filtrate was evaporated down to give a product that was treated with 50% TFA for 1 hr. After evaporation of TFA in vacua, the residue was dissolved in 2 ml MeCN, and treated with 100 mg MP-TsOH resin. The resin was washed thoroughly with THF, MeCN and MeOH,

and then treated with 2M NH_3 in MeoH to give AF2 (R^1=Me, R^3=cyclohexylmethyl and R^{15}=3-chlorophenyl).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e
246		316	317
247		316	317
248		316	317
249		329	330
250		329	330

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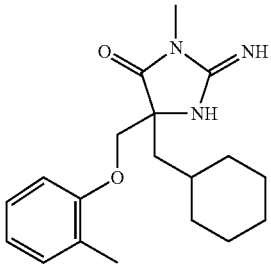
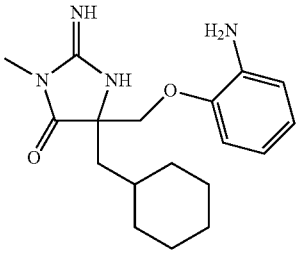
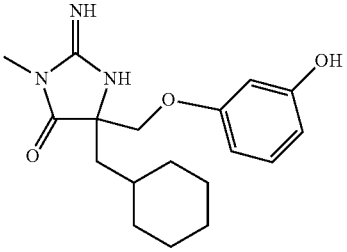
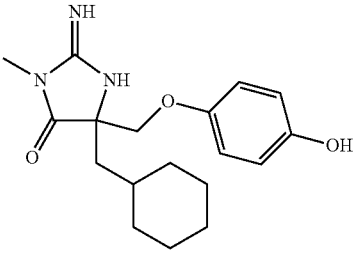
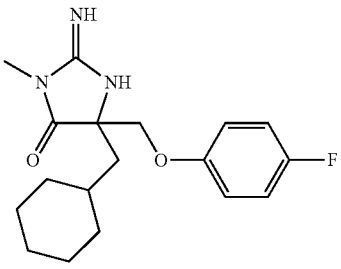
#	Structure	MW	Obs. m/e
251		329	330
252		330	331
253		331	332
254		331	332
255		333	334

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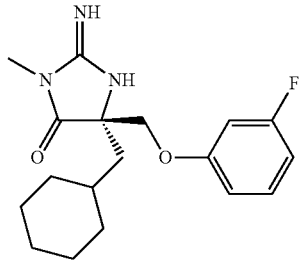
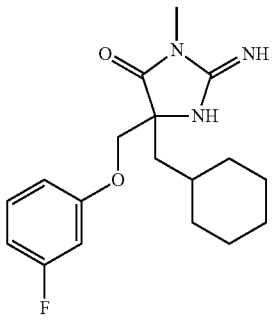
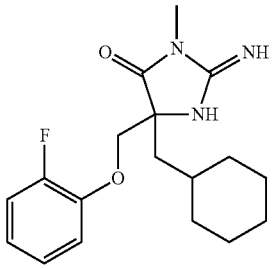
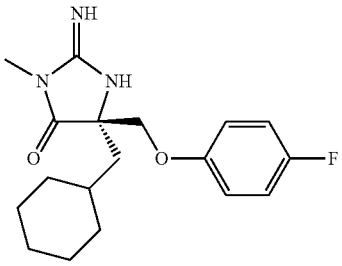
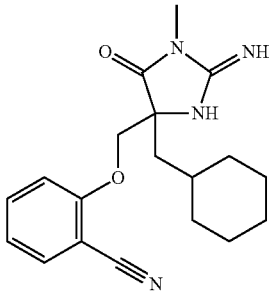
#	Structure	MW	Obs. m/e
256		333	334
257		333	334
258		333	334
259		333	334
260		340	341

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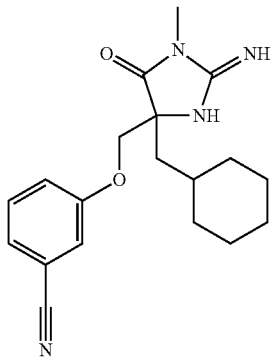
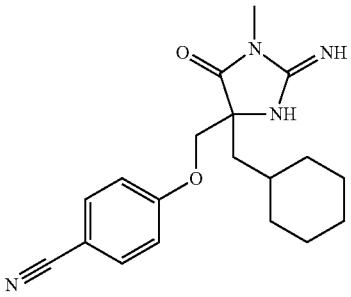
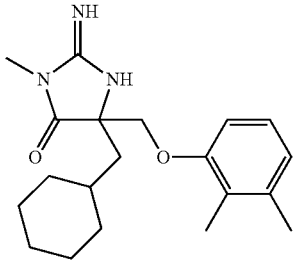
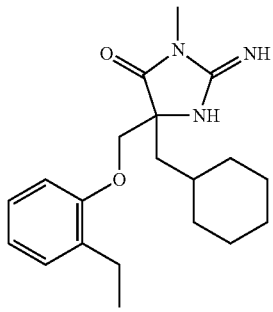
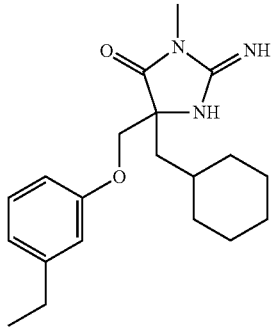
#	Structure	MW	Obs. m/e
261		340	341
262		340	341
263		343	344
264		343	344
265		343	344

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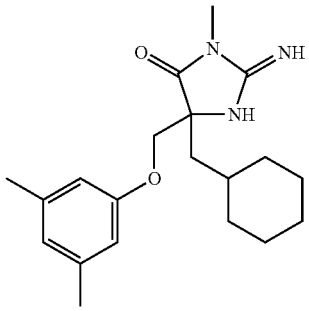
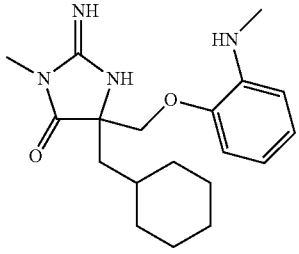
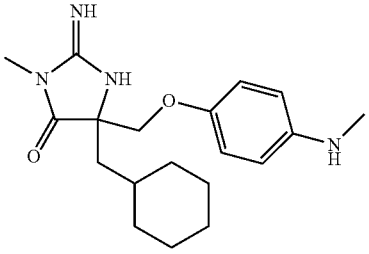
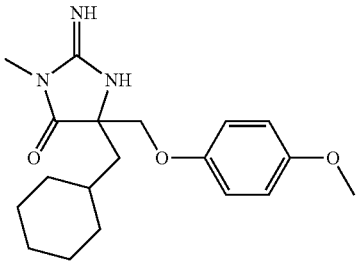
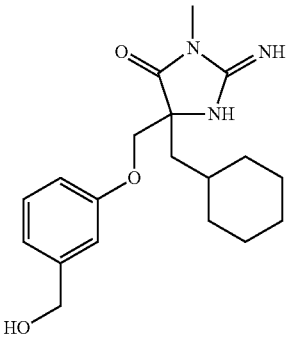
#	Structure	MW	Obs. m/e
266		343	344
267		344	345
268		344	345
269		345	346
270		345	346

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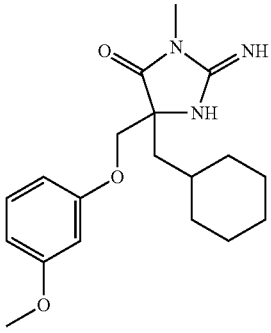
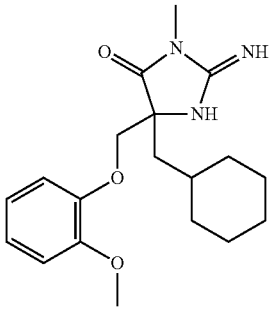
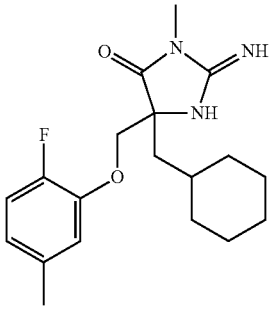
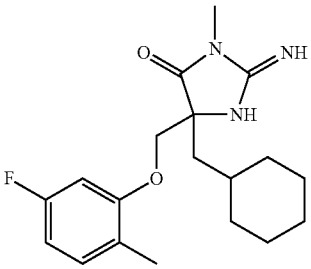
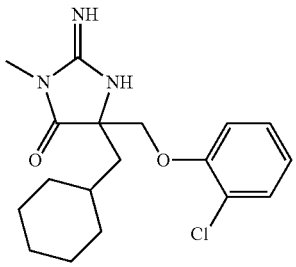
#	Structure	MW	Obs. m/e
271		345	346
272		345	346
273		347	348
274		347	348
275		349	350

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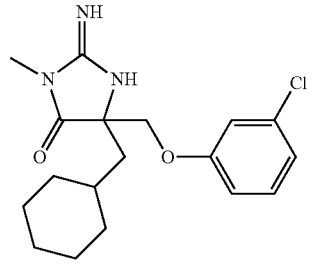
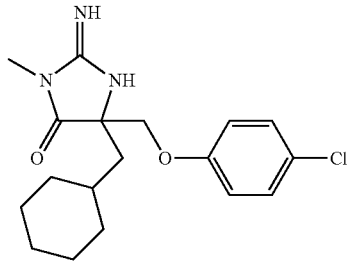
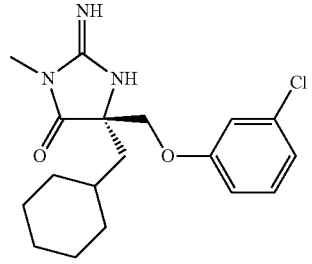
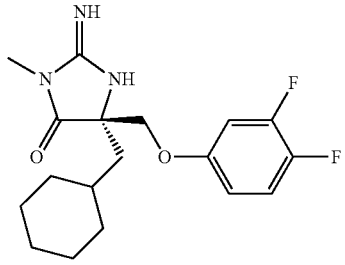
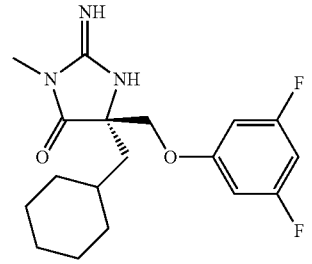
#	Structure	MW	Obs. m/e
276		349	350
277		349	350
278		349	350
279		351	352
280		351	352

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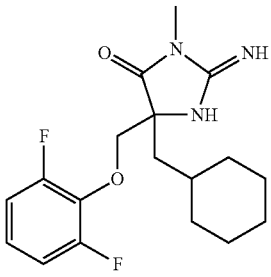
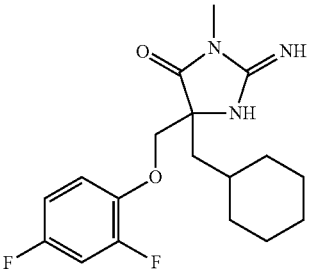
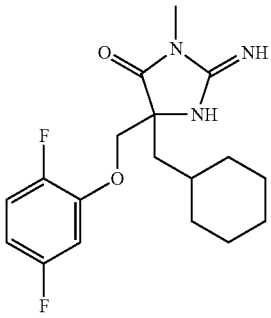
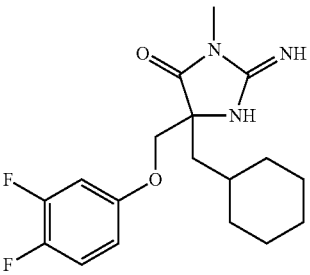
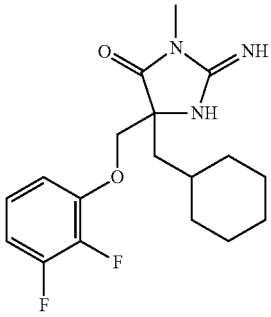
#	Structure	MW	Obs. m/e
281		351	352
282		351	352
283		351	352
284		351	352
285		351	352

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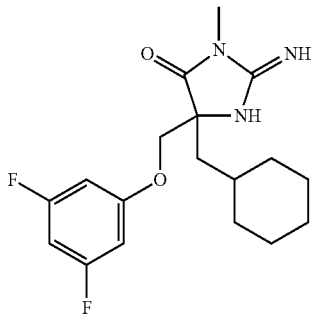
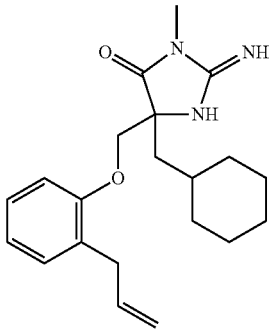
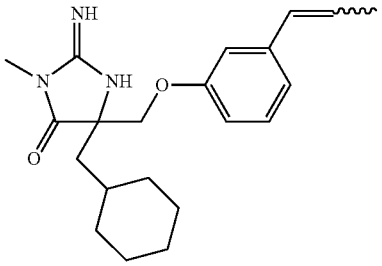
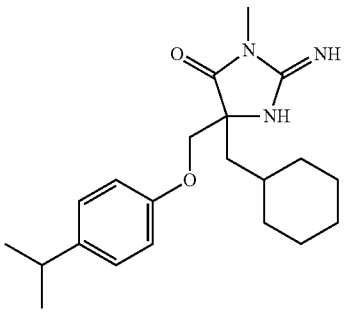
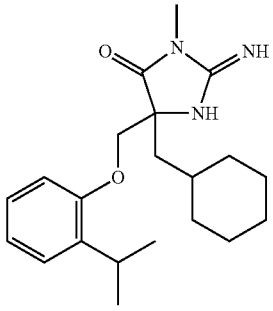
#	Structure	MW	Obs. m/e
286		351	352
287		355	356
288		355	356
289		357	358
290		357	358

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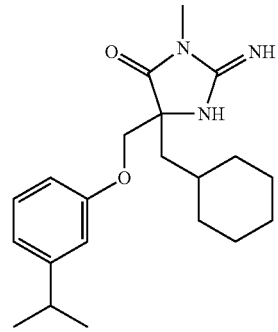
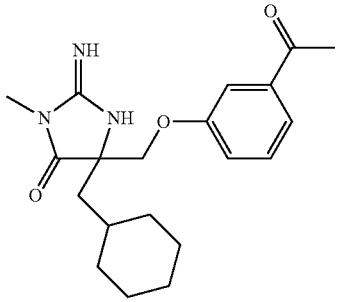
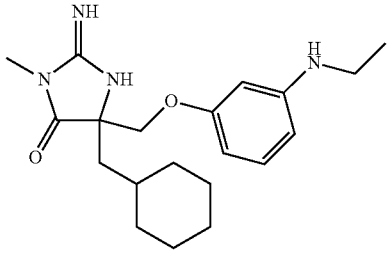
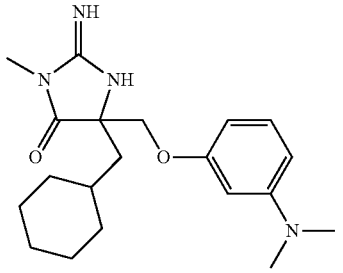
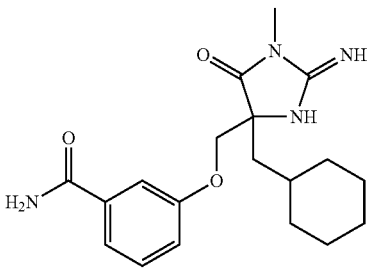
#	Structure	MW	Obs. m/e
291		357	358
292		357	358
293		358	359
294		358	359
295		358	359

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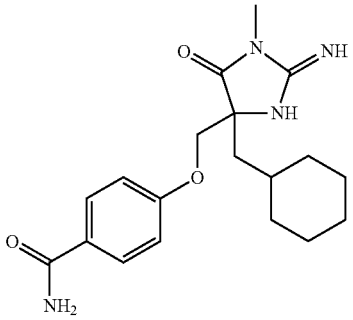
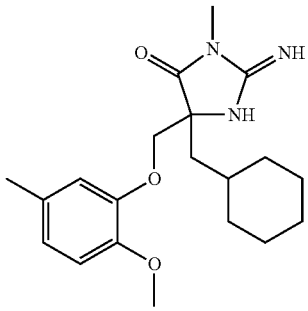
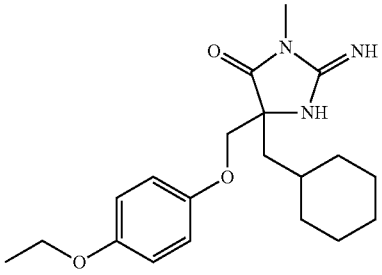
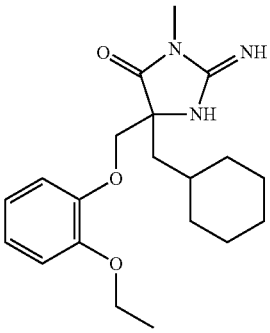
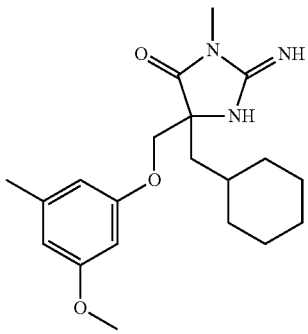
#	Structure	MW	Obs. m/e
296		358	359
297		359	360
298		359	360
299		359	360
300		359	360

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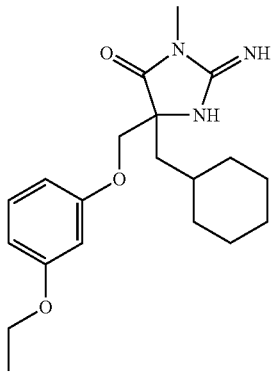
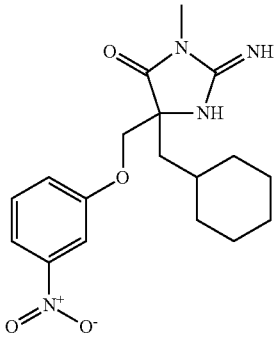
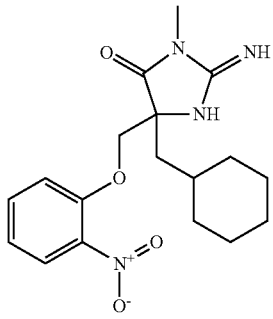
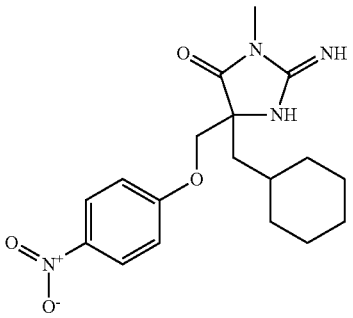
#	Structure	MW	Obs. m/e
301		359	360
302		360	361
303		360	361
304		360	361

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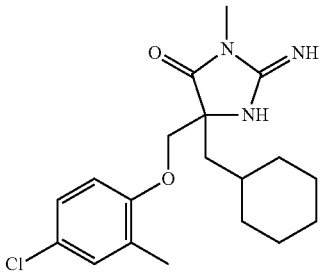
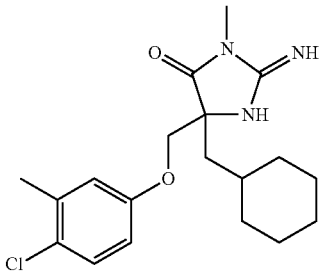
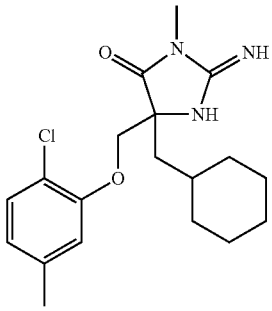
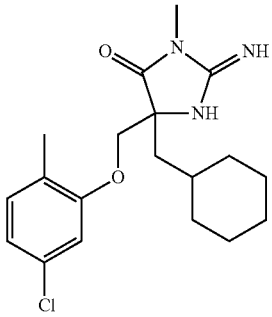
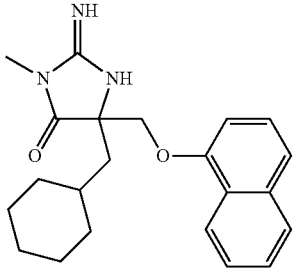
#	Structure	MW	Obs. m/e
305		363	364
306		363	364
307		363	364
308		363	364
309		365	366

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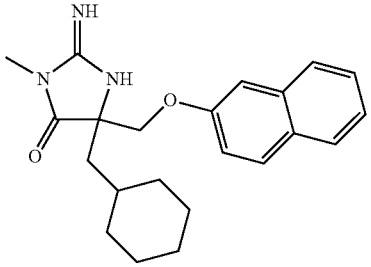
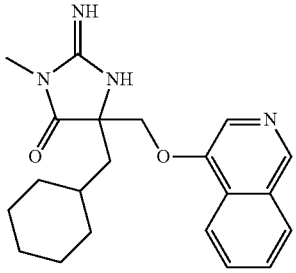
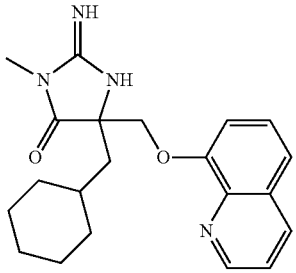
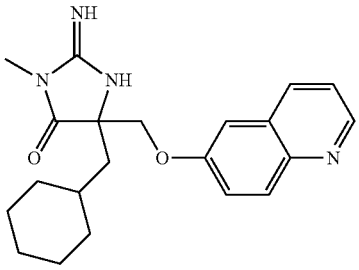
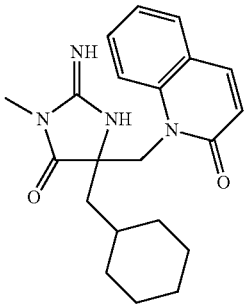
#	Structure	MW	Obs. m/e
310		365	366
311		366	367
312		366	367
313		366	367
314		366	367

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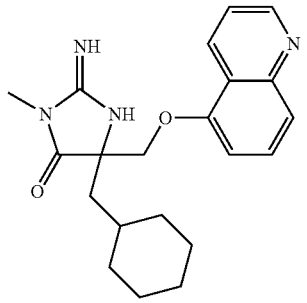
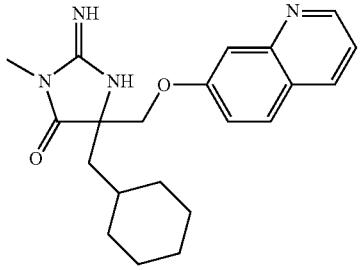
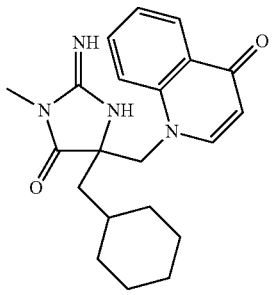
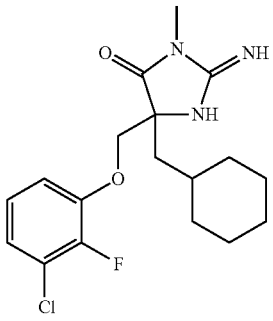
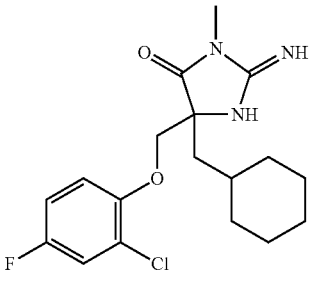
#	Structure	MW	Obs. m/e
315		366	367
316		366	367
317		366	367
318		367	368
319		367	368

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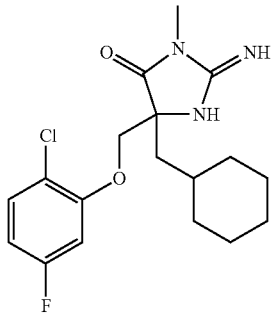
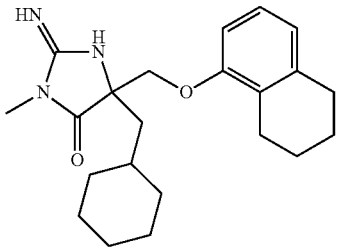
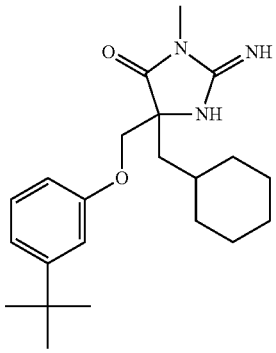
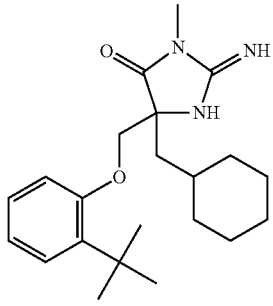
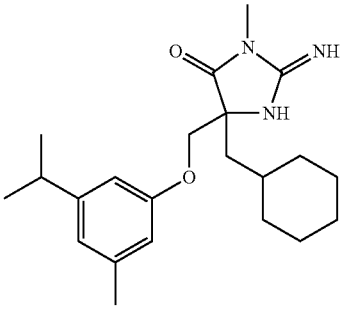
#	Structure	MW	Obs. m/e
320		367	368
321		369	370
322		371	372
323		371	372
324		371	372

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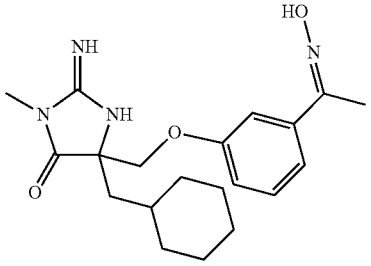
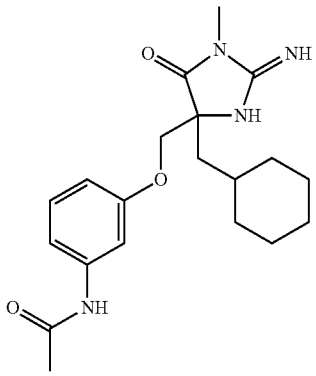
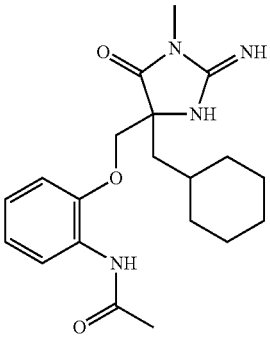
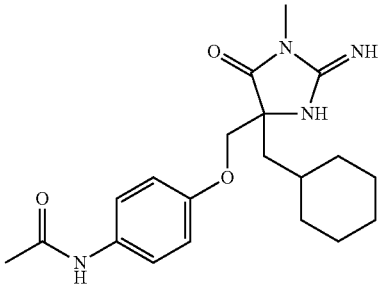
#	Structure	MW	Obs. m/e
325		372	373
326		372	373
327		372	373
328		372	373

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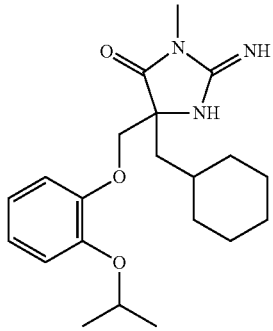
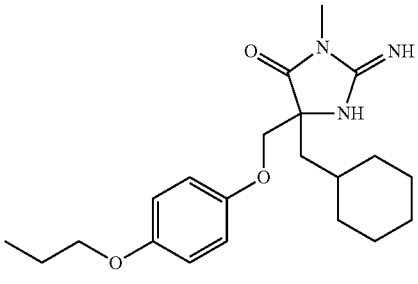
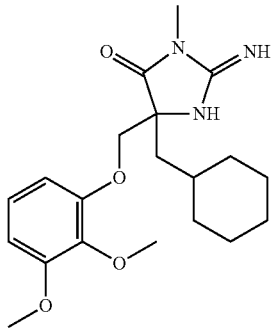
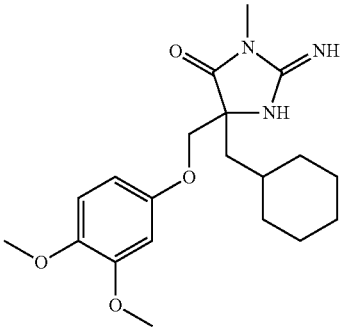
#	Structure	MW	Obs. m/e
329		373	374
330		373	374
331		375	376
332		375	376

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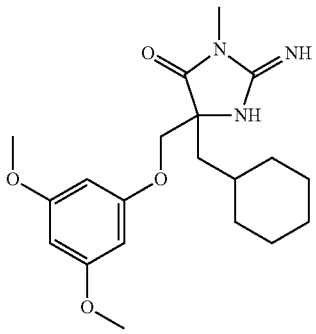
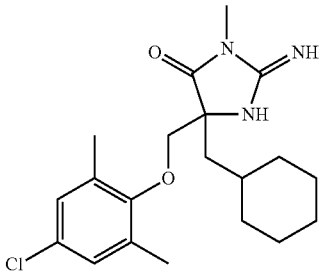
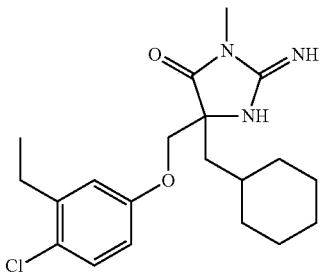
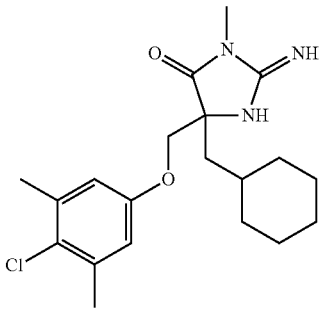
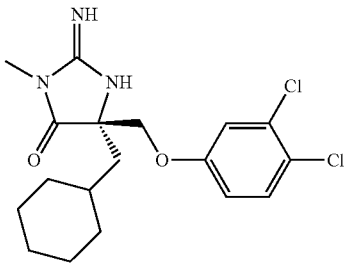
#	Structure	MW	Obs. m/e
333		375	376
334		377	378
335		377	378
336		377	378
337		383	384

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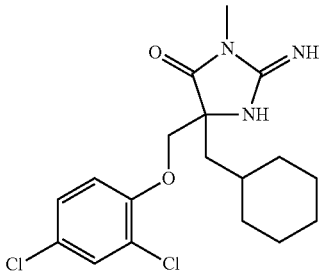
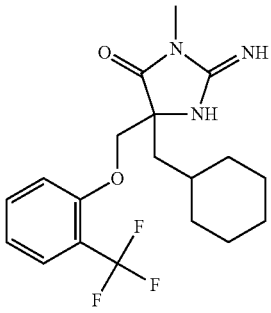
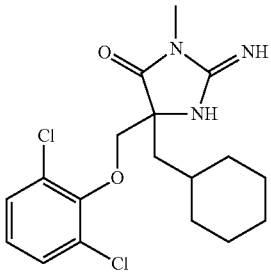
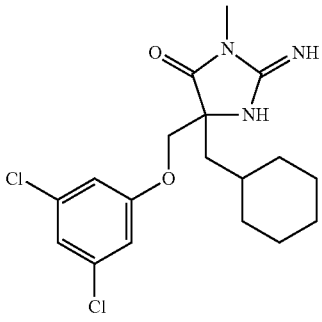
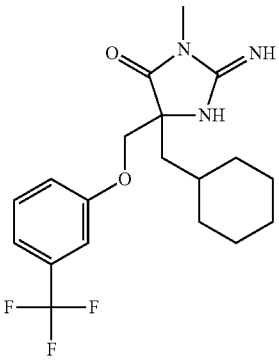
#	Structure	MW	Obs. m/e
338		383	384
339		383	384
340		383	384
341		383	384
342		383	384

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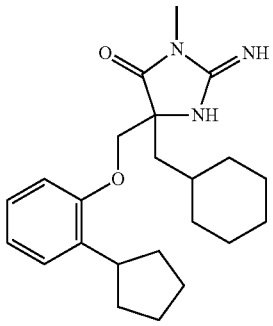
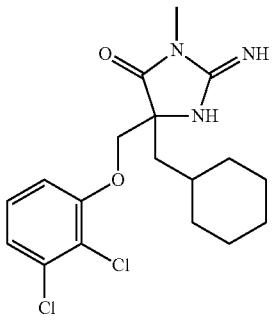
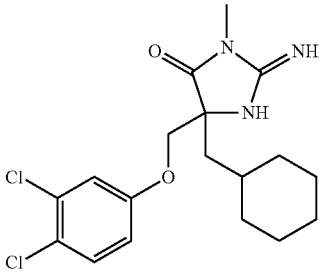
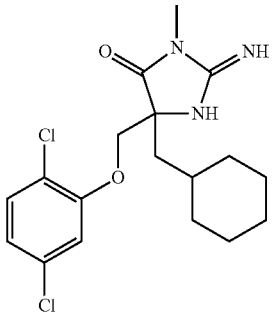
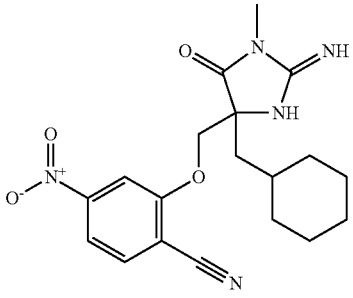
#	Structure	MW	Obs. m/e
343		383	384
344		383	384
345		383	384
346		383	384
347		385	386

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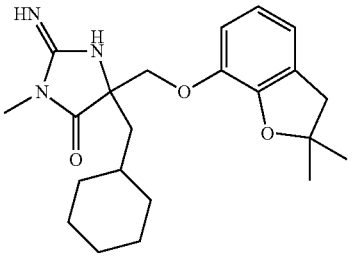
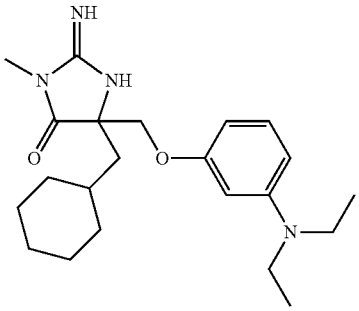
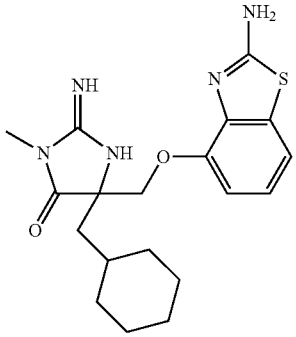
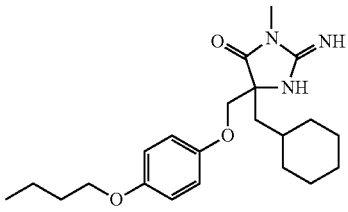
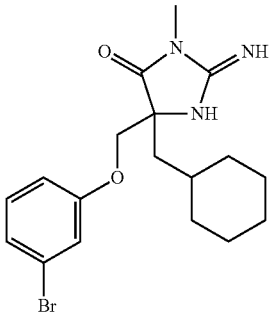
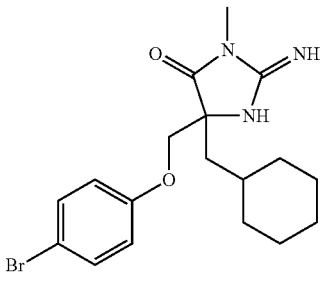
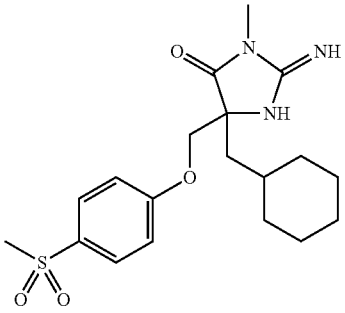
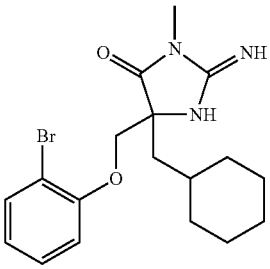
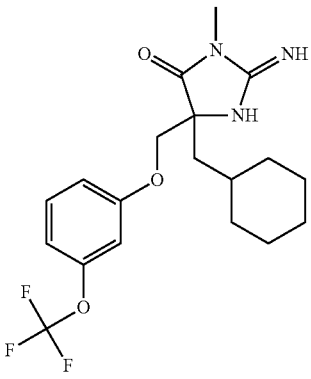
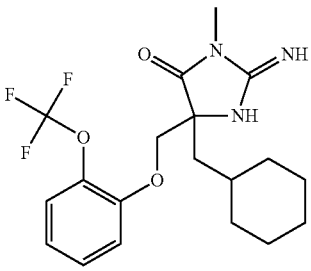
#	Structure	MW	Obs. m/e
348		385	386
349		386	387
350		387	388
351		387	388
352		393	394

#	Structure	MW	Obs. m/e
353		393	394
354		393	394
355		393	394
356		399	400
357		399	400

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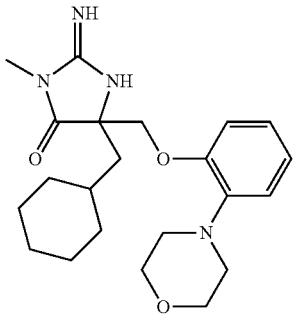
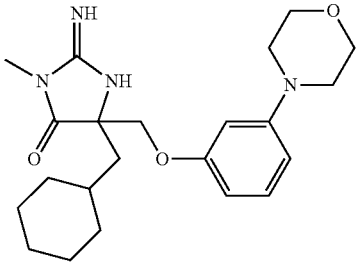
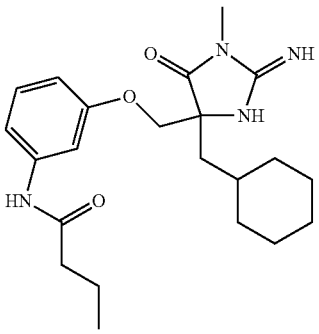
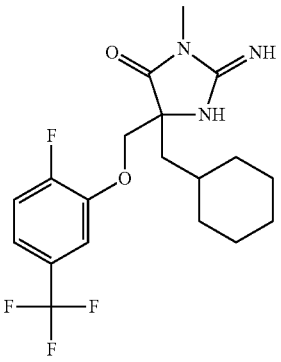
358		400	401
359		400	401
360		400	401
361		401	402

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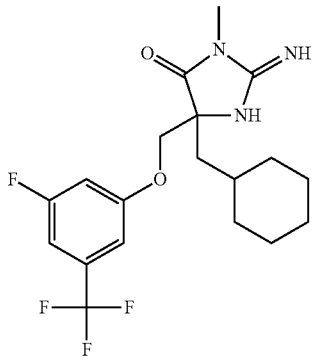
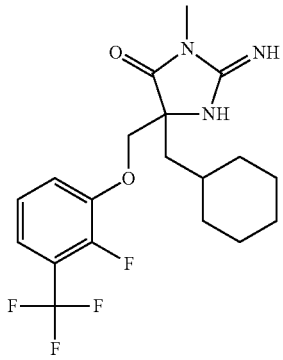
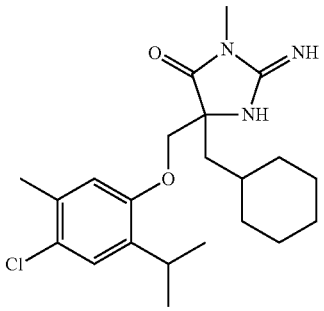
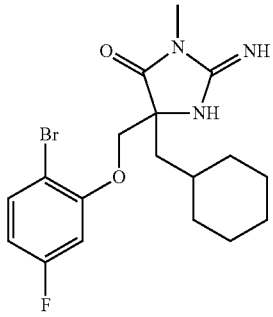
#	Structure	MW	Obs. m/e
362		401	402
363		401	402
364		405	406
365		411	412

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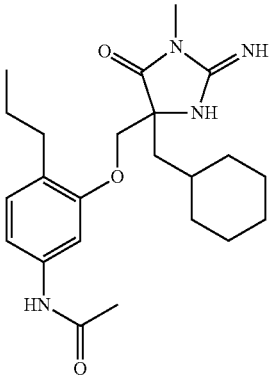
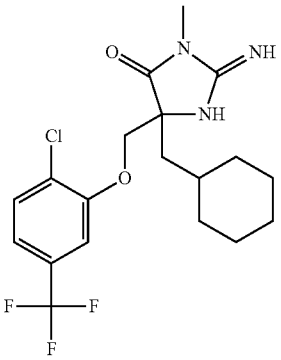
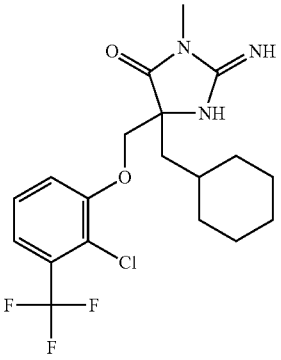
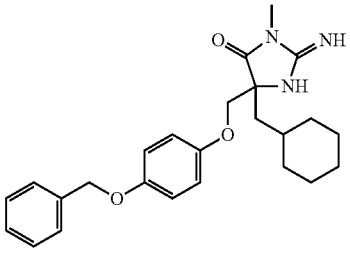
#	Structure	MW	Obs. m/e
366		414	415
367		417	418
368		417	418
369		421	422

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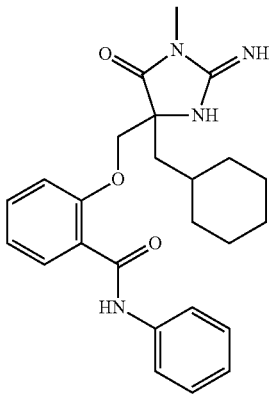
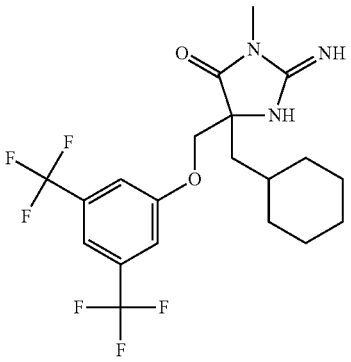
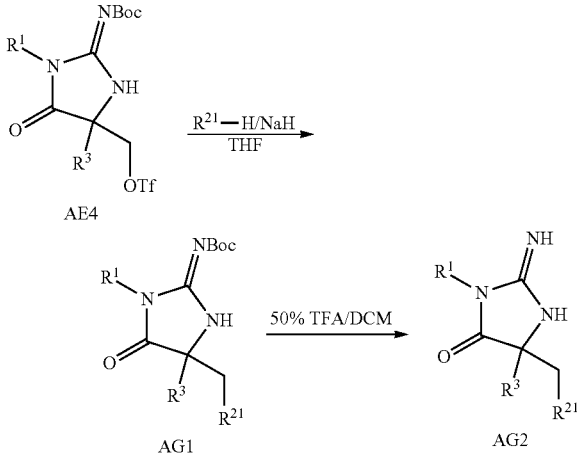
#	Structure	MW	Obs. m/e
370		434	435
371		451	452

Method AG



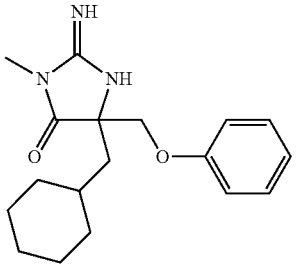
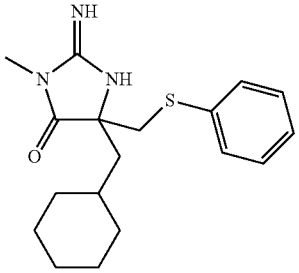
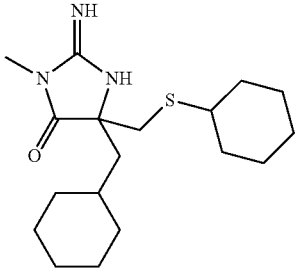
Method AG, Step 1:

R^{21}—H (R^{21}=PhS—) (33 μl, 0.318 mmole) was treated with NaH (10.2 mg, 60% in mineral oil) in 0.5 ml anhydrous THF. A solution of AE4 (R^1=Me, R^3=Cyclohexylmethyl) (20 mg, 0.0424 mmol) in 0.5 ml anhydrous THF was added. The reaction mixture was stirred at room temperature overnight before it was partitioned between ether and saturated $NaHCO_3$ water solution. The aqueous phase was extracted with ether 2 times. The combined organic phase was washed with brine 2 times, and dried over anhydrous $NaSO_4$. The crude was purified on flash column with EtOAc/hexane to give 9 mg of AG1 (R^{21}=PhS—, R^1=Me, R^3=cyclohexylmethyl) (49.2% yield).

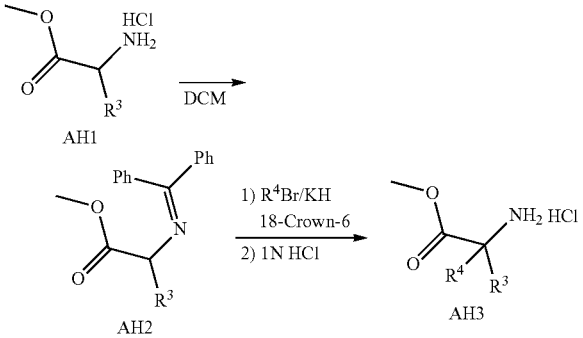
Method AG, Step 2:

AG1 (R^{21}=PhS—, R^1=Me, R^3=cyclohexylmethyl) was treated with 50% TFA according to the Step 6 of the method H to give AG2 (R^{21}=PhS—, R^1=Me, R^3=cyclohexylmethyl).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e
372		315	316
373		331	332
374		337	338

Method AH



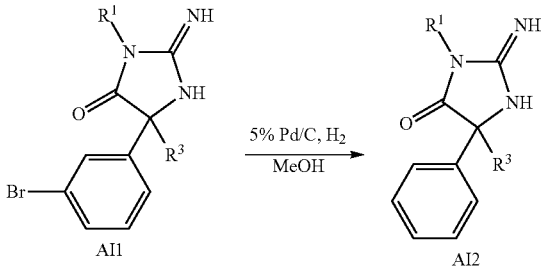
Method AH, Step 1:

Benzophenone imine (3.27 g, 18.04 mmole) was added to a suspension of AH1 (R^3=cyclohexylmethyl) (4 g, 18.04 mmole) in 65 ml DCM. The reaction mixture was stirred at room temperature overnight under N_2 before the solid was filtered, and the solvent was evaporated. The residue was dissolved in 100 ml ether, washed with water 2× and dried over anhydrous $MgSO_4$. The crude was purified on flash column to give 5.08 g (80.57% yield) of AH2 (R^3=cyclohexyl methyl).

Method AH, Step 2:

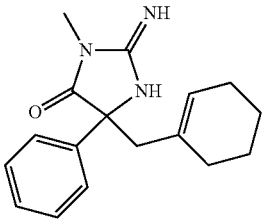
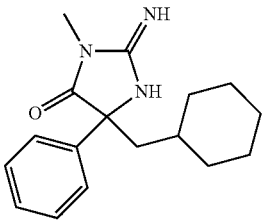
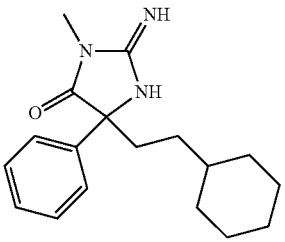
A solution of AH2 (R^3=cyclohexylmethyl) (1 g, 2.86 mmole) in 12 ml anhydrous THF was added to a suspension of 18-crown-6 (0.76 g, 2.86 mmole) and 30% KH in mineral oil (1.16 g, 8.58 mmole) in 4 ml anhydrous THF under N2. The mixture was cooled in ice-bath and R^4Br (R^4=3-pyridylmethyl, as a hydrobromide salt) was then added. The reaction mixture was stirred in ice-bath for 30 min and at room temperature for 2 more hrs before the reaction was quenched with 2 ml of HOAc/THF/H_2O (0.25:0.75:1). The mixture was diluted with 40 ml EtOAc/H_2O (1:1). The aqueous phase was extracted with EtOAc 3 times. The combined organic phase was washed with brine 3 times and dried over anhydrous MgSO4. The crude was purified on flash column to give 0.44 g (35.14% yield) of product which was treated with 1N HCl (2.2 ml, 2.22 mmole) in 3 ml ether in ice-bath followed by stirred at r.t. overnight. The aqueous phase was evaporated and purified on C-18 reverse phase column to give 0.22 g (66% yield) of AH3 (R^4=3-pyridylmethyl; R^3=cyclohexylmethyl).

Method AI



To a solution of compound AI1 (R^1=Me, R^3=n-Bu) (34 mg, 0.105 mmol) in methanol (1 ml) was added 10% Pd/C (5 mg). The mixture was kept under an H_2 balloon for 1 hr. After filtration of the catalyst, the filtrate was concentrated to get crude product. This residue was purified by RP HPLC to get compound AI2 (R^1=Me, R^3=n-Bu) (25 mg, 100%). Observed MW (M+H) 246.1; exact mass 245.15. ^{1}H NMR (400 MHz, CD_3OD): δ=7.59 (m, 2H), 7.36 (m, 3H), 3.17 (s, 3H), 2.17 (m, 2H), 1.27 (m, 4H), 0.86 (t, 3H, J=7.2 Hz).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e
375		283	284
376		285	286
377		299	300

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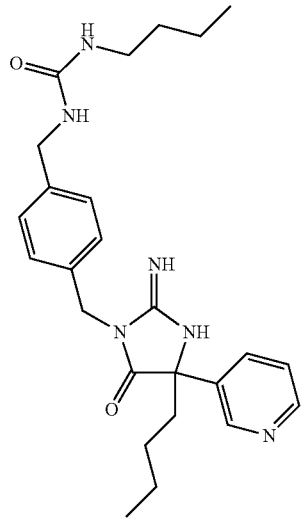
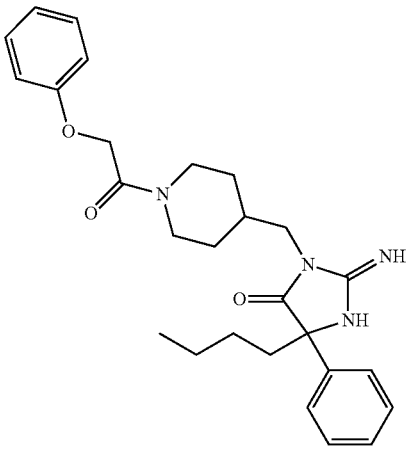
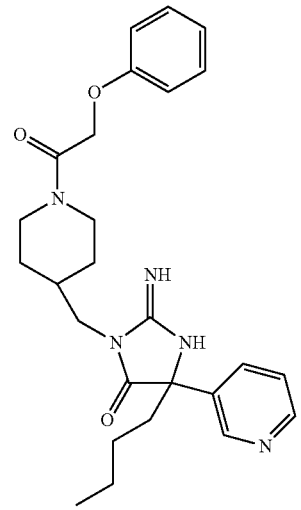
#	Structure	MW	Obs. m/e
378		450	451
379		462	463
380		463	464

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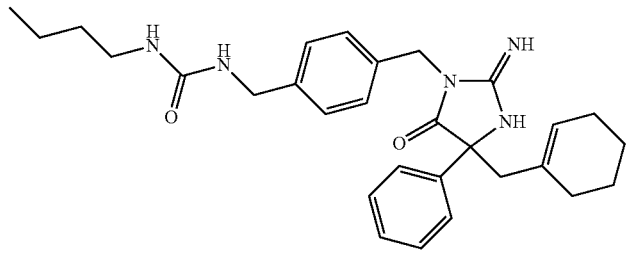
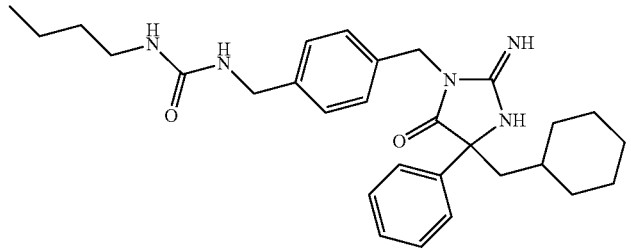
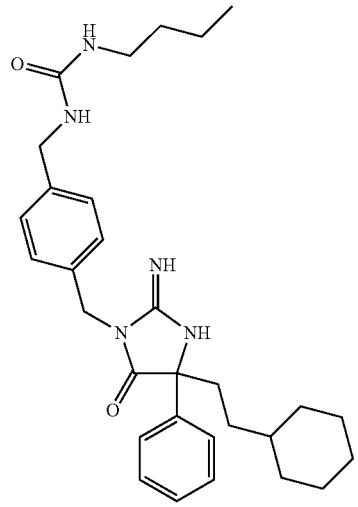
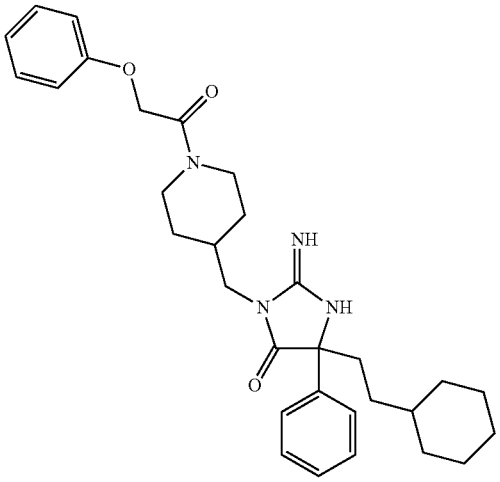
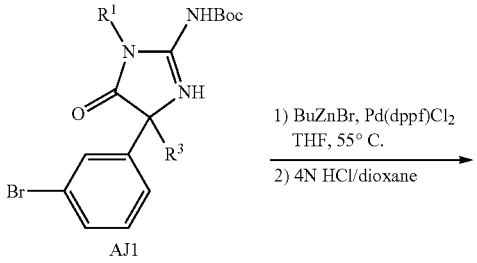
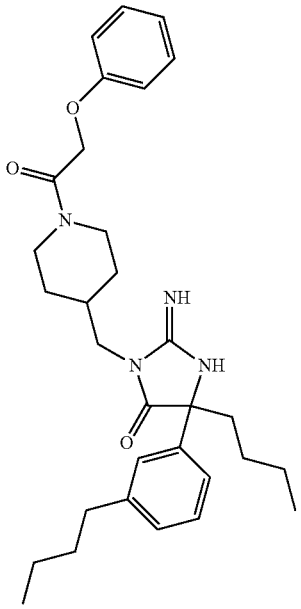
#	Structure	MW	Obs. m/e
381		487	488
382		489	490
383		503	504
384		516	517

Method AJ

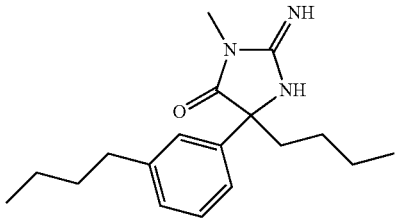


To a mixture of compound AJ1 (R^1=Me, R^3=n-Bu) (70 mg, 0.165 mmol) and butylzincbromide (1.32 ml, 0.6 mmol) was added $Pd(dppf)Cl_2$. The mixture was degassed, sealed and heated at 55° C. for 1 day. The mixture was diluted with CH_2Cl_2 and NH_3/H_2O. The organic layer was separated, dried, concentrated, and purified by RP HPLC to get product which was then treated with 4N HCl/dioxane for 30 min to give compound AJ2(R^1=Me, R^3=n-Bu) (12 mg, 25%). Observed MW (M+H) 302.1; ^{1}H NMR (400 MHz, CD_3OD): δ=7.32 (m, 3H), 7.22 (m, 1H), 3.19 (s, 3H), 2.65 (m, 2H), 2.20 (m, 2H), 1.60 (m, 2H), 1.38 (m, 4H), 1.24 (m, 2H), 0.92 (m, 6H).

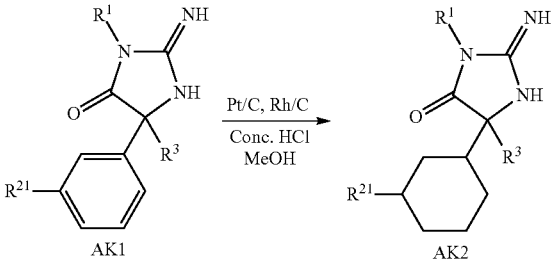
The following compound was synthesized in a similar fashion:

#	Structure	MW	Obs. m/e
386		518	519

-continued

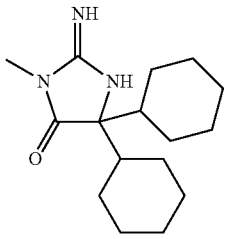
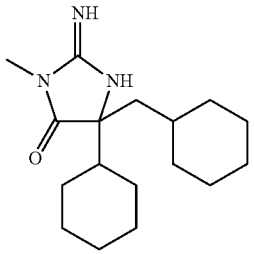
#	Structure	MW	Obs. m/e
385		301	302

Method AK

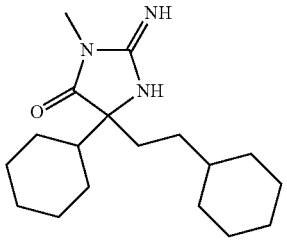
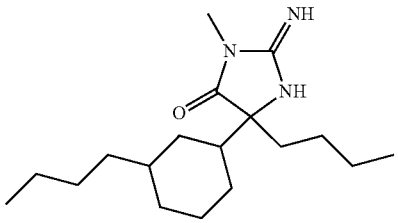
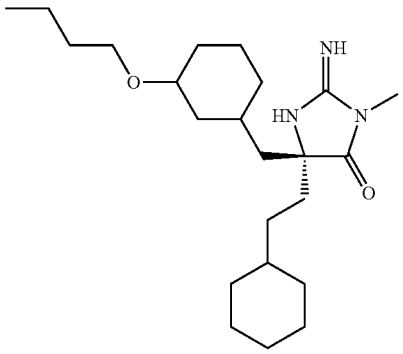
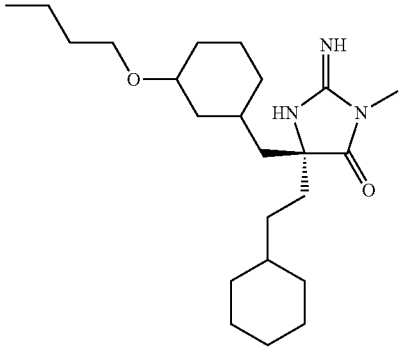


To a solution of AK1 (R^1=Me, R^3=n-Butyl, R^{21}=n-Bu) (9 mg, 0.03 mmol) in methanol (1 ml) was added 5% Pt/C (5 mg), Rh/C (5 mg) and conc. HCl (0.05 ml). The mixture was kept under H_2 (50 psi) for 2 days. After the filtration of the catalyst, the filtrate was concentrated to get compound AK2 (R^1=Me, R^3=n-butyl, R^{21}=n-Bu) Observed MW (M+H) 308.1. ^{1}H NMR (CD_3OD): 6=3.16 (s, 3H), 1.80 (m, 6H), 1.26 (m, 16H), 0.88 (m, 6H).

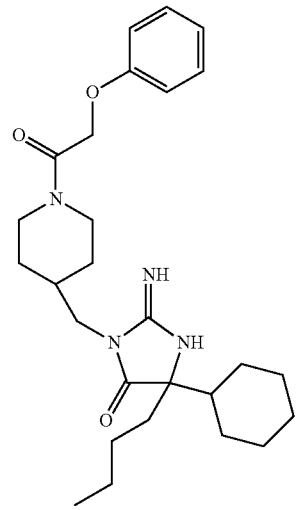
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e
387		277	278
388		291	292

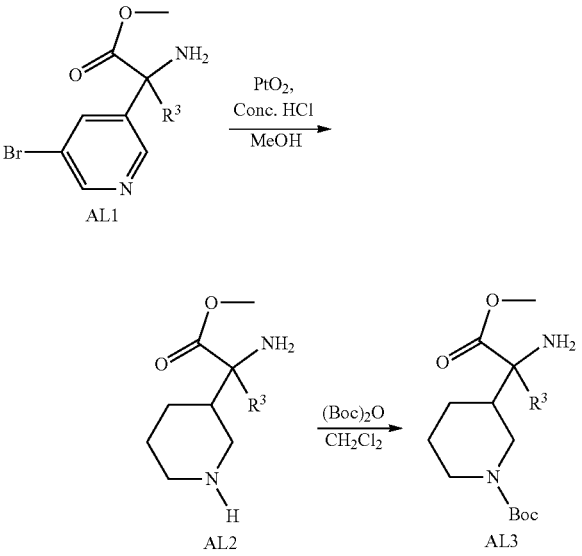
-continued

#	Structure	MW	Obs. m/e
389		305	306
390		307	308
391		391	392
392		391	392

-continued

#	Structure	MW	Obs. m/e
393		468	469

Method AL



Method AL, Step 1:

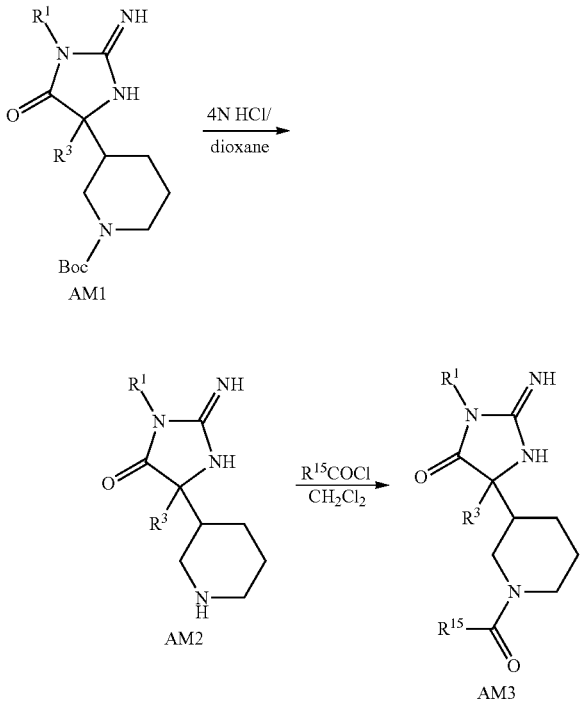
To a solution of compound AL1 (R^3=n-Bu) (418 mg, 1.39 mmol) in methanol (8 ml) was added PtO_2 (40 mg) and conc. HCl (0.4 ml). The mixture was hydrogenated (50 psi) for 1 day. After filtration of the catalyst, the filtrate was concentrated. The crude residue was basified to pH=11-12 by 1N NaOH. This mixture was extracted with ethyl acetate. The organic layer was separated, dried and concentrated to get compound AL2 (R^3=n-Bu) (316 mg, 100%).

Method AL, Step 2:

To a solution of compound AL2 (R^3=n-Bu) (300 mg, 1.32 mmol) in dichloromethane (6 ml) was added $(BOC)_2O$ (316

mg, 1.45 mmol). The mixture was stirred at RT for 1.5 hr. It was diluted with water and dichloromethane. The organic layer was separated, dried and concentrated to get compound AL3 (R^3=n-Bu) (464 mg, 100%).

Method AM



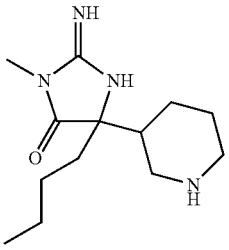
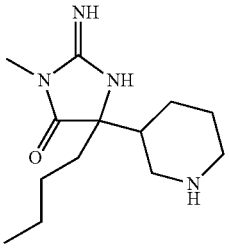
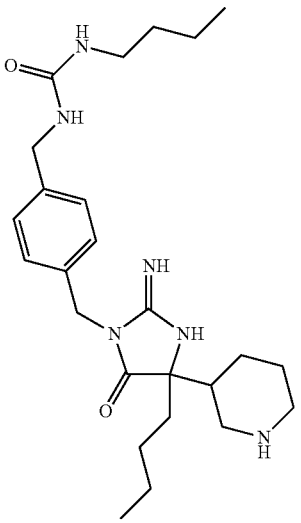
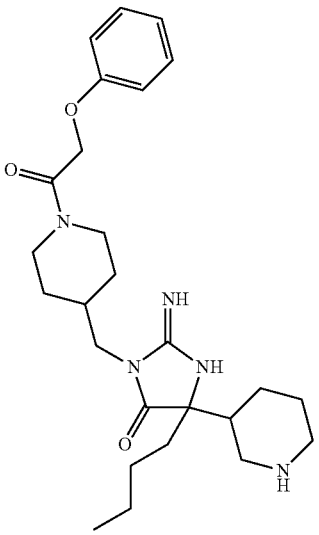
Method AM, Step 1:

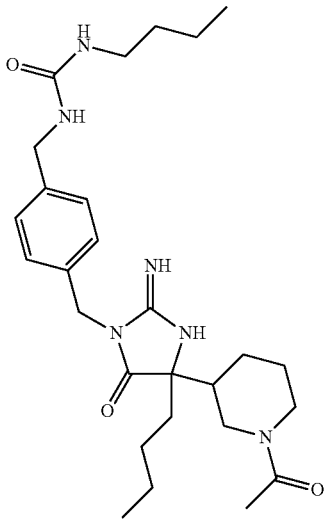
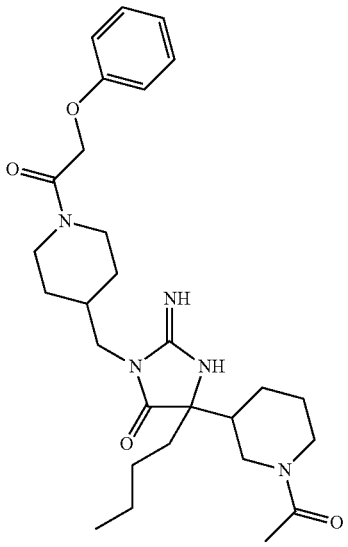
Compound AM1 (R^1=Me, R^3=n-Butyl) was treated with 4N HCl in dioxane for 2 hr. The mixture was concentrated to get compound AM2 as an HCl salt (R^1=Me, R^3=n-Butyl). Observed MW (M+H) 470.1; ^{1}H NMR (CD_3OD): δ=7.28 (m, 2H), 6.96 (m, 3H), 4.80 (m, 2H), 4.56 (m, 1H), 4.00 (m, 1H), 3.64 (m, 4H), 3.37 (m, 2H), 3.12 (m, 1H), 3.00 (m, 1H), 2.90 (m, 1H), 2.72 (m, 1H), 2.38 (m, 1H), 2.12-1.62 (m, 8H), 1.35 (m, 6H), 1.12 (m, 1H), 0.91 (m, 3H).

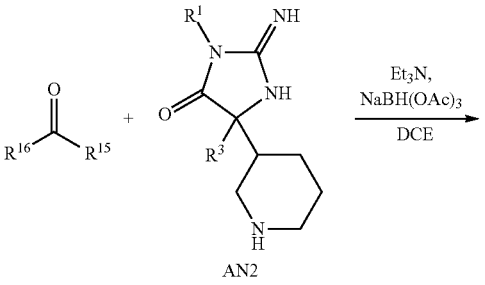
Method AM, Step 2:

To a solution of compound AM2 (R^1=Me, R^3=n-Butyl) (32 mg, 0.068 mmol) in dichloromethane (1 ml) was added acetyl chloride (5 ul, 0.072 mmol). The mixture was stirred for 2 hr. It was then diluted with CH_2Cl_2 and water. The organic layer was separated, dried, concentrated and purified by RP HPLC to get compound AM3 (R^1=Me, R^3=n-Butyl and R^{15}=Me) Observed MW (M+H) 512.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27 (m, 2H), 6.98 (m, 1H), 6.92 (m, 2H), 4.65 (s, 2H), 4.50 (m, 2H), 3.98 (m, 1H), 3.70 (m, 1H), 3.41 (m, 2H), 2.98 (m, 2H), 2.62 (m, 1H), 2.50 (m, 1H), 2.47 (m, 1H), 2.02 (m, 5H), 1.75 (m, 6H), 1.26 (m, 7H), 0.84 (m, 3H).

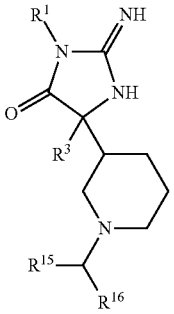
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e
394		252	253
395		252	253
396		456	457
397		469	470

#	Structure	MW	Obs. m/e
398		498	499
399		511	512



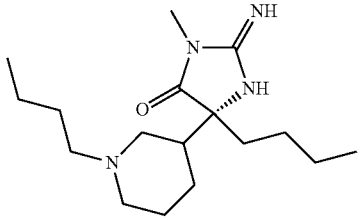
AN2



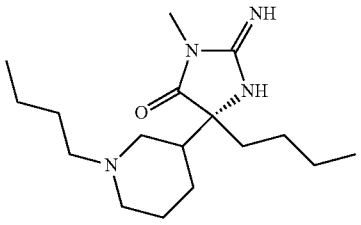
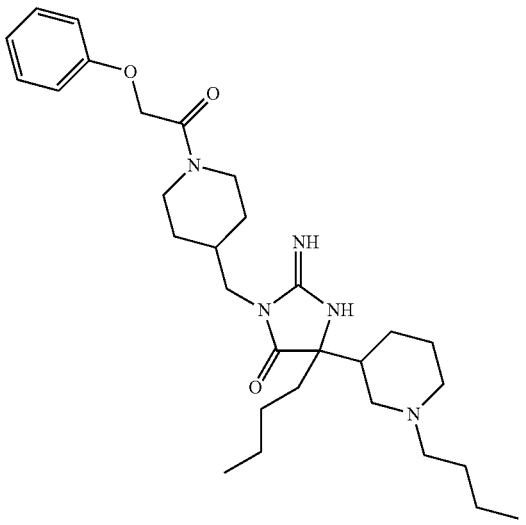
AN3

To a solution of compound AN2 (R^1=4-N-(α-phenoxyacetyl)piperidinylmethyl, R^3=n-Butyl) (28 mg, 0.06 mmol) in dichloroethane (2 ml) was added butyraldehyde (5.3 ul, 0.06 mmol), triethylamine (8.4 ul, 0.06 mmol) and NaBH$(OAc)_3$ (18 mg, 0.084 mmol). The mixture was stirred overnight. It was then diluted with dichloromethane and water. The organic layer was separated, dried, concentrated and purified by RP HPLC to get AN2 (R^1=4-N-(a-phenoxyacetyl) piperidinylmethyl, R^3=n-Butyl, R^{15}=propyl and R^{16}=H) (5.4 mg, 17%). Observed MW (M+H) 526.1; exact mass 525.37. ^{1}H NMR (CD_3OD): δ=7.28 (m, 2H), 6.96 (m, 3H), 4.76 (m, 2H), 4.55 (m, 1H), 4.05 (m, 1H), 3.77 (m, 1H), 3.61 (m, 3H), 3.50 (m, 1H), 3.11 (m, 4H), 2.85 (m, 1H), 2.68 (m, 1H), 2.38 (m, 1H), 2.05 (m, 2H), 1.95 (m, 2H), 1.73 (m, 5H), 1.39 (m, 8H), 1.10 (m, 1H), 0.99 (m, 3H), 0.92 (m, 3H).

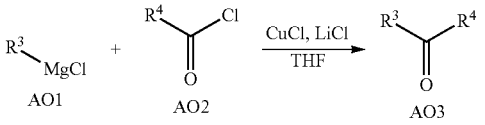
The following compound was synthesized using similar method:

#	Structure	MW	Obs. m/e
400		308	309

-continued

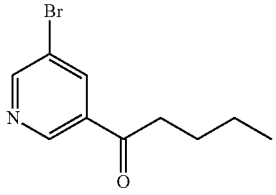
#	Structure	MW	Obs. m/e
401		308	309
402		525	526

Method AO

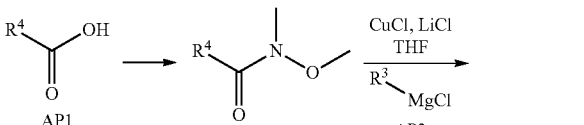


A mixture of copper chloride (2.06 g, 20.8 mmol) and lithium chloride (1.76 g, 41.6 mmol) in 100 ml of THF was cooled down to −78° C. To this mixture, a 2.0M solution of AO1 (R^3=n-butyl) (10 ml, 20 mmol) was added gradually. The reaction was warmed up to −60° C., and AO2 (R^4=m-Br-Ph) (2.9 ml, 22 mmol) was injected. The mixture was stirred at −60° C. for 15 minutes and then quickly warmed up to RT by removing the dry-ice bath. The reaction was quenched with water and sat. $NaHCO_3$. After addition of diethyl ether, a lot of precipitate formed and was filtered. From the biphasic filtrate, the organic layer was separated, dried, concentrated and purified by silica gel chromatography (10% EtOAc/hexane) to get ketone AO3 (R^4=m-BrPh, R^3=n-Bu) (3.93 g, 82%). Observed MW (M+H) 241.1; exact mass 240.01. ^1H NMR (400 MHz, $CDCl_3$): δ=8.07 (m, 1H), 7.88 (m, 1H), 7.64 (m, 1H), 7.34 (m, 1H), 2.94 (t, 3H, J=7.2 Hz), 1.71 (m, 2H), 1.40 (m, 2H), 0.95 (t, 3H, J=7.6 Hz).

The following ketones were made according to Method 9:

Structure	Observed MW (M + H)	Exact mass
	242.1	241.01

Method AP



Method AP, Step 1:

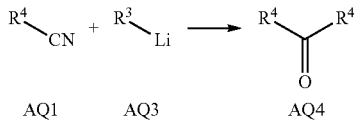
To a solution of AP1 (R^4=3-Bromophenyl) (5 g, 25 mmol) in dichloromethane (10 ml) were added N,O-dimethylhy-

droxylamine hydrochloride (2.56 g, 26.25 mmol) and 4-methylmorpholine (2.95 ml, 26.25 mmol). EDCl (5.04 g, 26.25 mmol) was then added portionwise. The reaction mixture was stirred at RT overnight and was then quenched with 1N HCl (60 ml). The mixture was extracted with dichloromethane. The organic layer was washed with 1N HCl and brine, dried over Na_2SO_4, and concentrated to give the Weinreb amide AP2 (R^4=m-BromoPhenyl) (5.96 g, 98%). Observed MW (M+H) 244.1; exact mass 243.99. ^{1}H NMR ($CDCl_3$): δ=7.78 (m, 1H), 7.58 (m, 2H), 7.24 (m, 1H), 3.51 (s, 3H), 3.32 (s, 3H). This material was used in the next step without purification.

Method AP, Step 2:

To a suspension of magnesium turnings (1.19 g, 48.8 mmol) in 30 ml of THF was added dropwise a solution of R^3Br (R^3=cyclohexylethyl) (5.73 ml, 36.6 mmol) in 24 ml of THF. After addition of half of the solution of bromide, several crystals of iodine were added to initiate the reaction. The mixture became cloudy and heat evolved. The rest of the solution of bromide was added dropwise. The mixture was stirred at RT for 30 minutes and then was cooled to 0° C., and the AP2 (R^4=m-BromoPhenyl) (5.96 g, 24.4 mmol) was added. The mixture was stirred at RT for 3 hr and then quenched with 1N HCl until no residual Mg(0) was left. The phases was separated, and the water layer was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The crude was purified by silica chromatography (15% EtOAc/hexane) to get ketone AP3 (R^4=m-BromoPhenyl, R^3=Cyclohexylethyl) (8.06 g, 100%). Observed MW (M+H) 295.2; exact mass 294.06. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.18 (m, 1H), 7.85 (m, 1H), 7.64 (m, 1H), 7.33 (m, 1H), 2.94 (t, 3H, J=7.2 Hz), 1.70 (m, 9H), 1.63 (m, 4H).

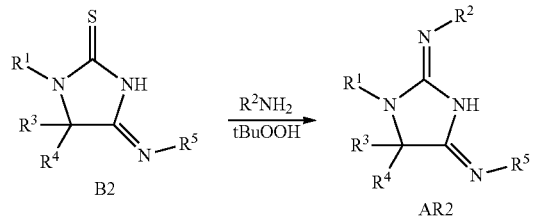
Method AQ



AQ1 AQ3 AQ4

To a −78° C. solution of AQ1 (R^4=cyclopropyl) (2.55 g, 38.0 mmol) in diethyl ether (100 ml) was added AQ2 (R^3=n-BuLi) (38 ml, 1.5 M in hexanes, 57 mmol). After 45 min, the cooling bath was removed. After 3 h at RT, the reaction was quenched by dropwise addition of water and then diluted further with EtOAc and water. The phases were separated and the aqueous layer was extracted with EtOAc (2×). The organic portions were combined, washed with brine, dried over $MgSO_4$, and concentrated. This crude residue was subjected to column chromatography (silica gel, 0%→100% CH_2Cl_2/hexanes) to provide the desired ketone AQ4 (R^4=cyclopropyl, R^3=n-Butyl) (2.57 g, 20.4 mmol, 54%). ^{1}H NMR ($CDCl_3$) δ 2.52 (1, J=7.2 Hz, 2H), 1.90 (m, 1H), 1.57 (m, 2H), 1.30 (m, 2H), 0.98 (m, 2H), 0.89 (t, J=7.6 Hz, 3H), 0.83 (m, 2H).

Method AR

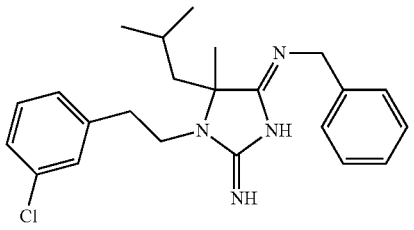
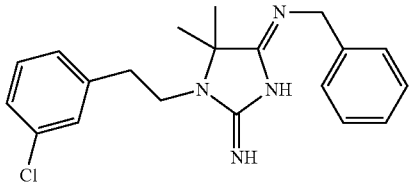
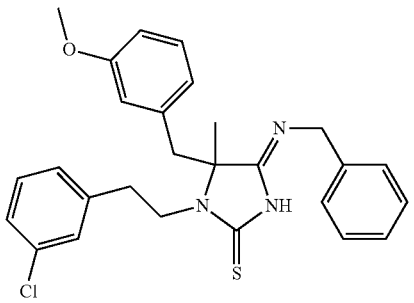
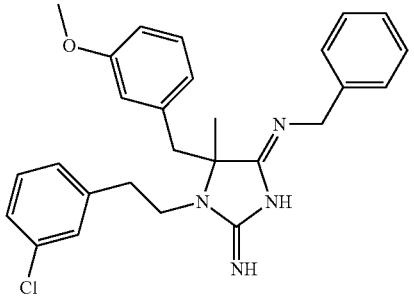


B2 AR2

Method AR:

Compound B2 (R^1=m-Cl-Phenethyl, R^3=Me, R^4=i-butyl and R^5=benzyl) was converted into AR^2 (R^1=m-Cl-Phenethyl, R^3=Me, R^4=i-butyl and R^5=benzyl) using method A step 3.

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e
403		396	397
404		354	NA
405		477	NA
406		460	NA

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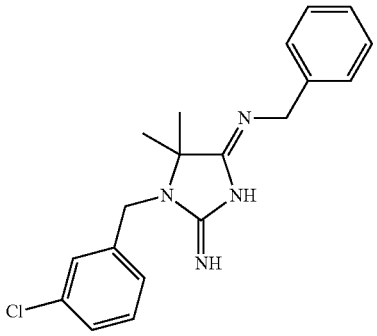
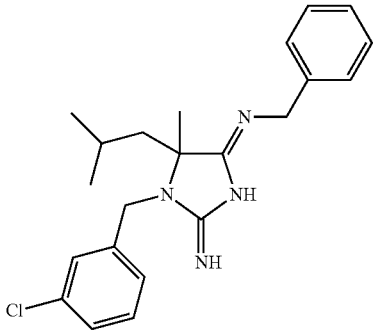
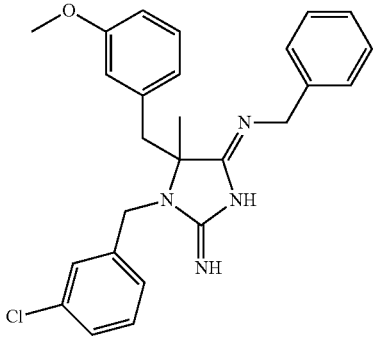
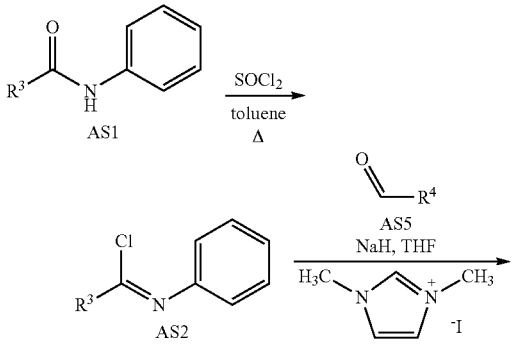
#	Structure	MW	Obs. m/e
407		340	NA
408		382	NA
409		446	NA

Method AS



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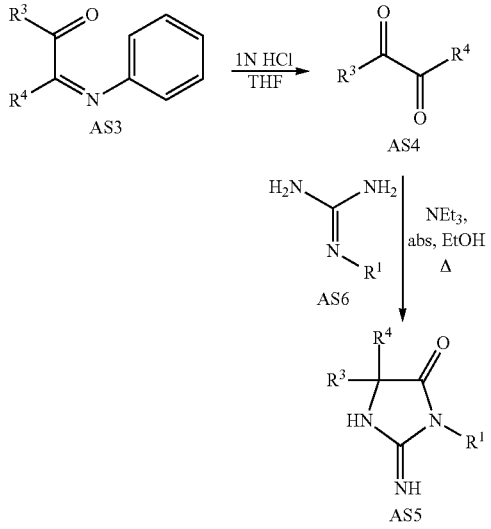


Method AS, Step 1:

To a mixture of AS1 (R^3=Ph) (3.94 g) in toluene (10 ml) was added thionyl chloride (1.61 ml) and the resulting mixture as heated under reflux for 6 h (until HCl evolution ceased). The reaction mixture was kept overnight at rt before it was concentrated in vacua. Toluene (10 ml) was added and the mixture was concentrated in vacuo again. The reaction mixture was dissolved in CH_2Cl_2, solid sodium bicarbonate added, filtered and then the CH_2Cl_2 solution was concentrated in vacuo to give AS2 (R^3=Ph).

Method AS, Step 2:

To AS2 (R^3=Ph) (0.645 g) and AS5 (R^4=4-chlorophenyl) (0.464 g), and 1,3-dimethylimidazolium iodide (0.225 g) in anhydrous THF (20 ml) was added 60% sodium hydride in oil (0.132 g). The resulting mixture was stirred at a for 18 h. The reaction mixture was concentrated and partitioned between H_2O and Et_2O. The dried Et_2O solution was concentrated in vacuo to give a yellow residue which was placed on preparative silica gel plates and eluted with CH_2Cl_2 to give AS3 (R^3=Ph, R^4=p-ClPh). (Miyashita, A., Matsuda, H., Hiagaskino, T., Chem. Pharm. Bull., 1992, 40 (10), 2627-2631).

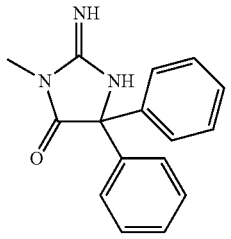
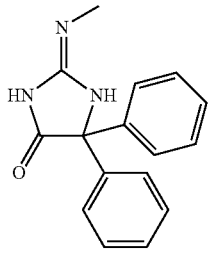
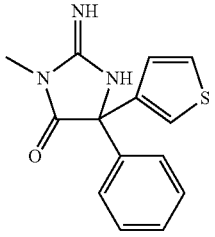
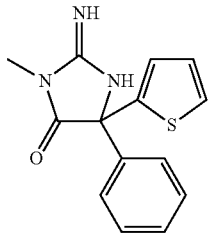
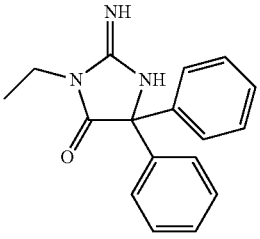
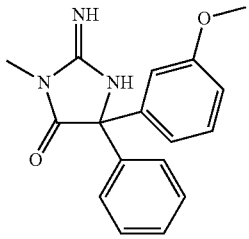
Method AS, Step 3:

Hydrochloric acid (1 N, 1.5 ml) was added to AS3 (R^3=Ph, R^4=p-ClPh) in THF (10 ml) and the resulting solution was stirred at rt for 20 h. The reaction mixture was concentrated in vacua and then partitioned between CH_2Cl_2 and H_2O. The dried CH_2Cl_2 was concentrated in vacuo to give a residue which was placed on preparative silica gel plates and eluted with CH_2Cl_2:hexane 1:1 to afford AS4 (R^3=Ph, R^4=p-ClPh).

Method AS, Step 4:

AS4 (RC-Ph, R^4=p-ClPh) (0.12 g) and methylguanidine, HCl (AS6, R^1=Me) (0.055 g) were mixed in absolute EtOH (5 ml) with triethylamine (0.2 ml) and then heated under reflux for 20 h. The resulting mixture was concentrated and then partitioned between CH_2Cl_2 and H_2O. The dried CH_2Cl_2 was concentrated in vacuo to give a residue which was placed on preparative silica gel plates and eluted with CH_2Cl_2:MeOH 9:1 to afford AS5 (R^3=Ph, R^4=p-ClPh and R^1=Me).

The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e
411		265	266
412		265	266
413		271	272
414		271	272
415		279	280
416		295	296

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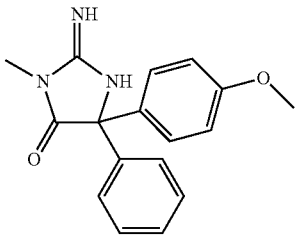
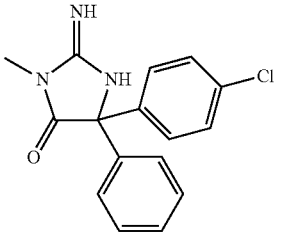
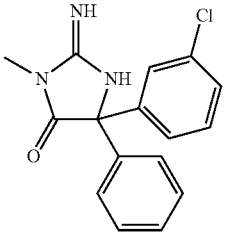
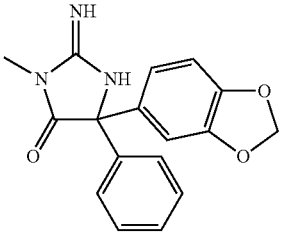
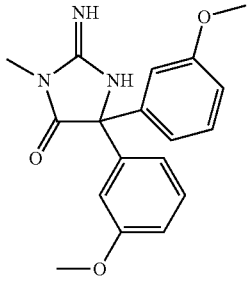
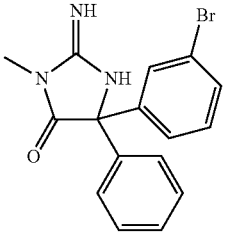
#	Structure	MW	Obs. m/e
417		295	296
418		299	300
419		299	300
420		309	310
421		325	326
422		343	344

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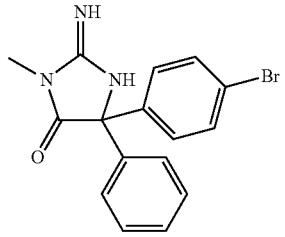
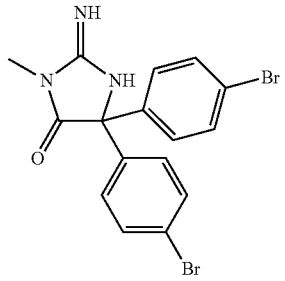
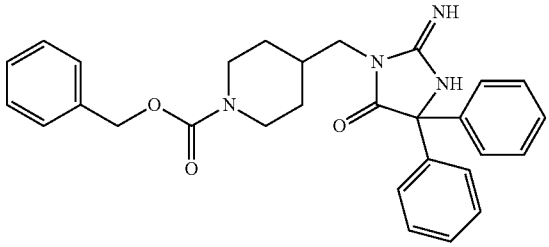
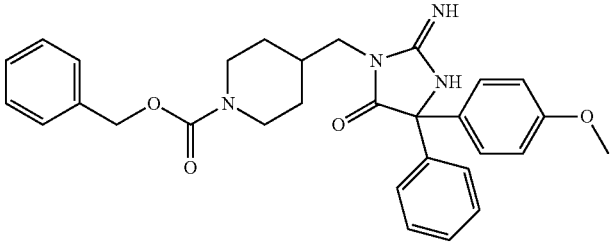
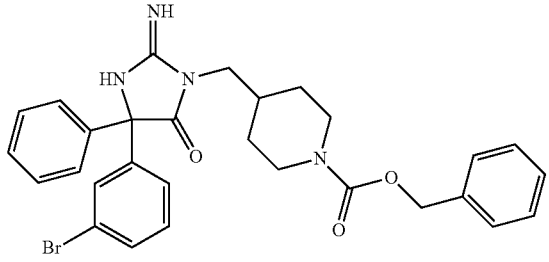
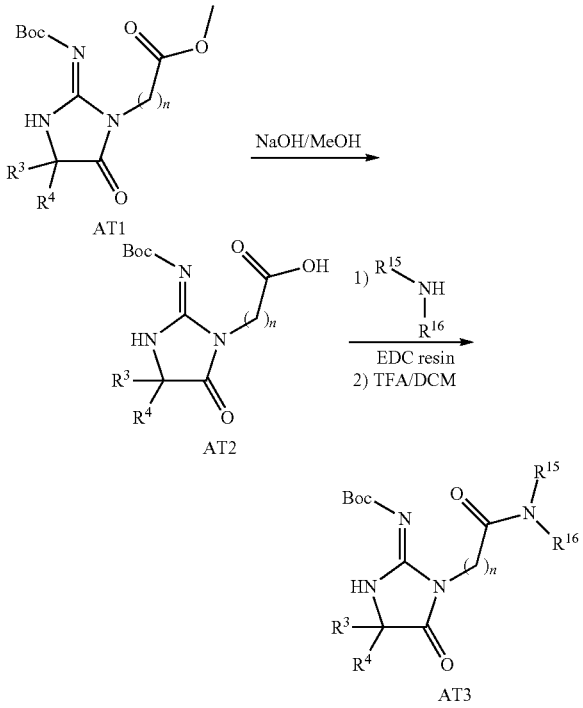
#	Structure	MW	Obs. m/e
423		343	344
424		421	422
425		482	483
426		512	513
427		560	561

Method AT



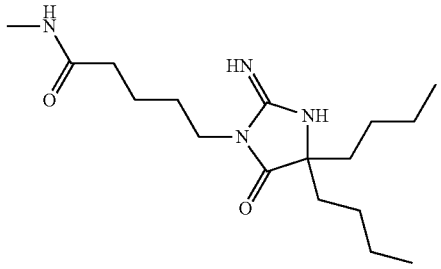
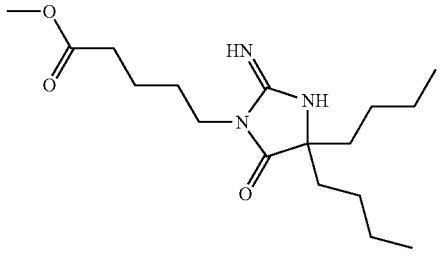
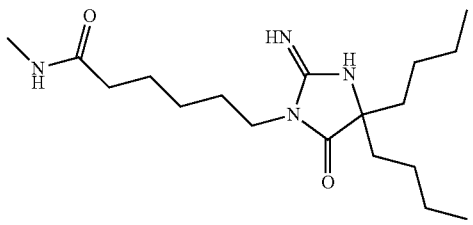
Method AT, Step 1:

AT1, prepared using a method similar to Method H, Step 1, 2 and 3, (n=4, R^3=R^4=n-Bu) (0.146 g) in MeOH (3 ml) and 1N NaOH (0.727 ml) were stirred overnight at rt. The mixture was concentrated and then partitioned in water (pH~3, adjusted using conc. HCl) and EtOAc. The dried EtOAc layer was concentrated in vacuo to afford AT2 (n=4, R^3=R^4=n-Bu).

Method AT, Step 2:

Compound AT2 (n=4, R^3=R^4=n-Bu) (0.012 g) in MeCN (1 ml) was treated with EDC resin (0.12 g, 1.44 mmol/g), HOBT (0.004 g) in THF (1 ml), and n-butylamine (R^{15}=H, R^{16}=n-butyl) (0.007 ml). The reaction was carried out overnight at rt. before Argonaut PS-NCO resin (0.150 g), PS-polyamine resin (0.120 g) and THF (2 ml) were added and the mixture shaken for 4 h. The reaction mixture was filtered and resin washed with THF (2 ml). The combined organic phase was concentrated in vacuo before the residue was treated with 1N HCl in MeOH (1 ml) for 4 h followed by evaporation of solvent to give AT3 (n=4, R^3=R^4=n-Bu, R^{16}=H and R^{16}=n-Butyl).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e
428		324	325
429		325	326
430		338	339

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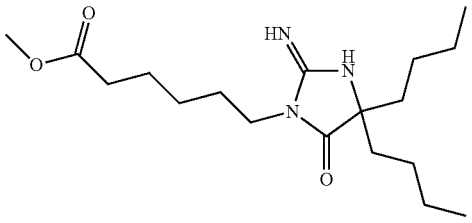
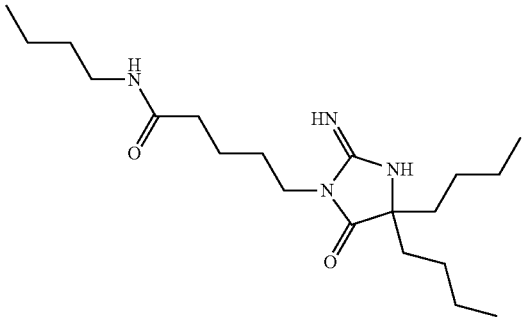
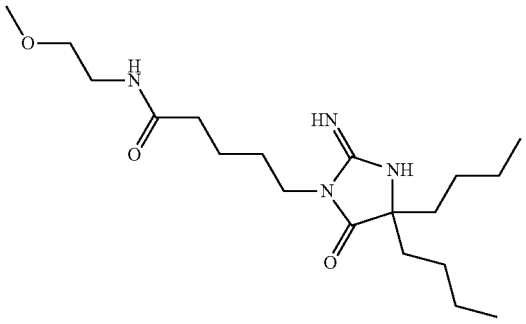
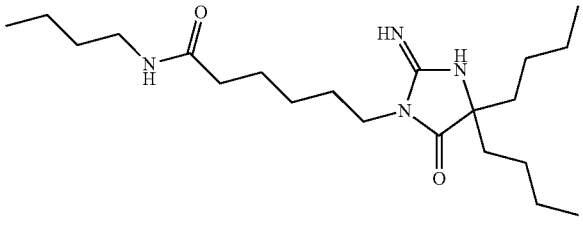
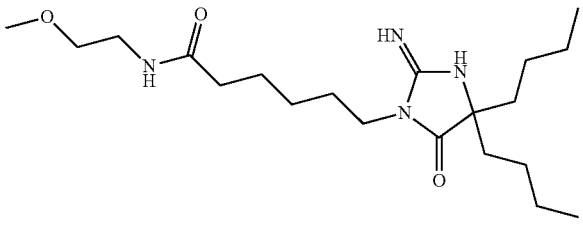
#	Structure	MW	Obs. m/e
431		339	340
432		366	367
433		368	369
434		380	381
435		382	383

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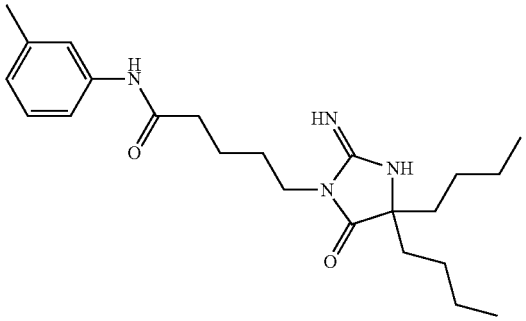
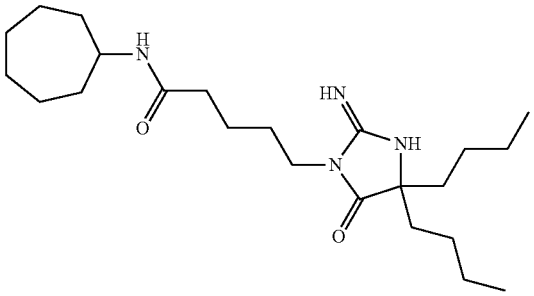
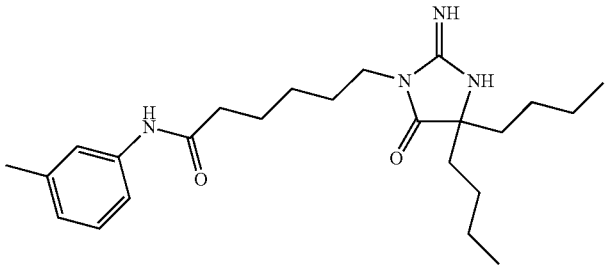
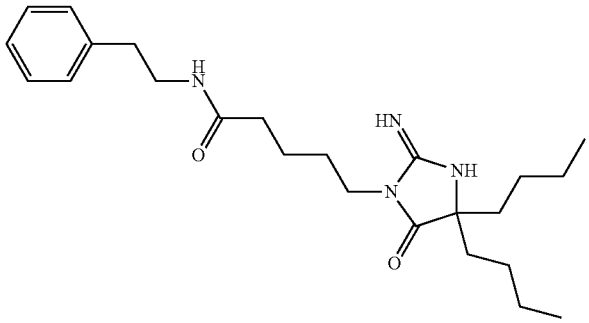
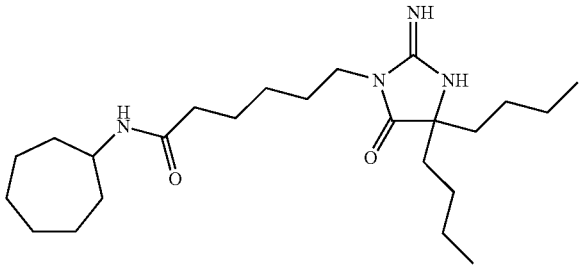
#	Structure	MW	Obs. m/e
436		400	401
437		406	07
438		414	15
439		414	15
440		420	21

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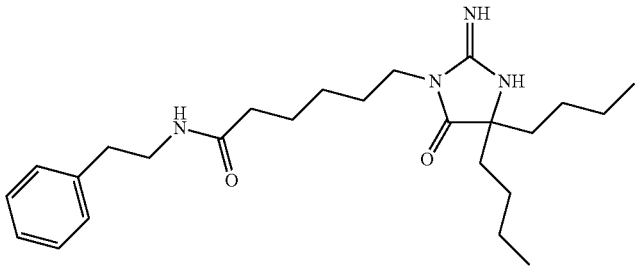
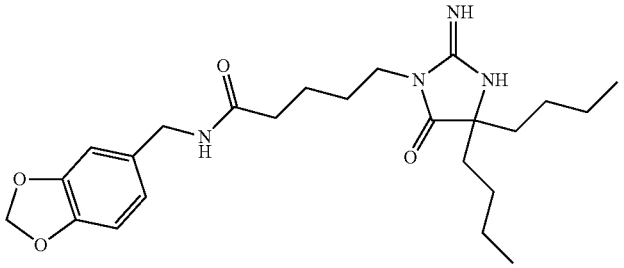
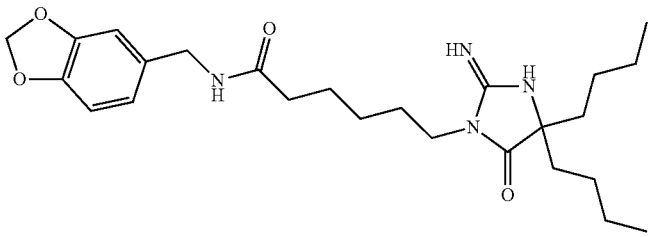
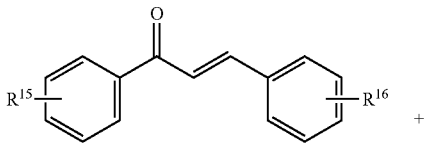
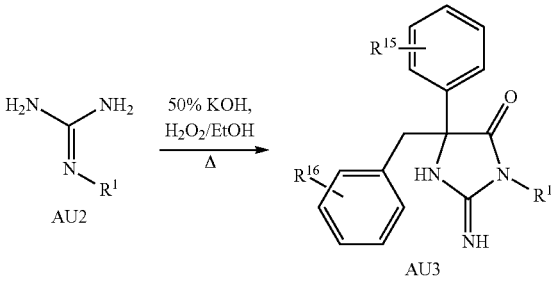
#	Structure	MW	Obs. m/e
441		428	29
442		444	45
443		458	59

Method AU



AU1



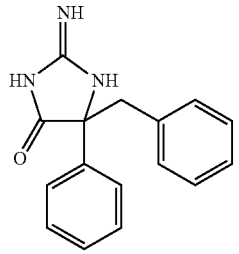
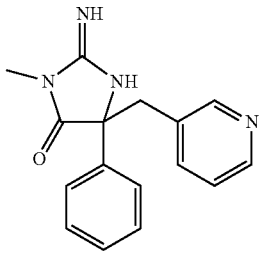
AU2

AU3

A published procedure was adapted (Varga, I.; Nagy, T.; Kovesdi, L; Benet-Buchholz, J.; Dormab, G.; Urge, L.; Darvas, F. Tetrahedron, 2003, (59) 655-662).

AU1 (R^{15}=H, R^{16}=H) (0.300 g), prepared according to procedure described by Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R., (*Vogel's Textbook of Practical Organic Chemistry.* 5th ed. Longman: new York, 1989; pp 1034-1035), AU2 (HCl salt, R^1=Me) (0.237 g), 50% KOH (0.305 ml), 30% H_2O_2 (0.115 ml) and EtOH (4.6 ml) were heated in a sealed tube for 2 h. Reaction mixture was concentrated and extracted with CH_2Cl_2. The dried organic solution was concentrated in vacuo to give a residue which was placed on preparative silica gel plates eluting with CH_2Cl_2:MeOH 9:1 to afford AU3 (R^{15}=H, R^{16}=H, R^1=Me).

The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e
444		265	266
446		280	281

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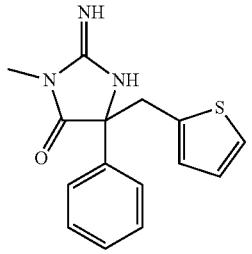
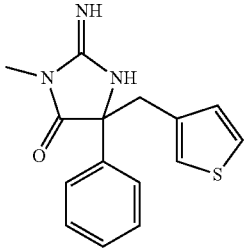
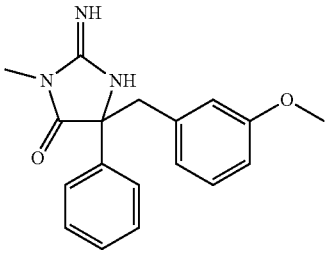
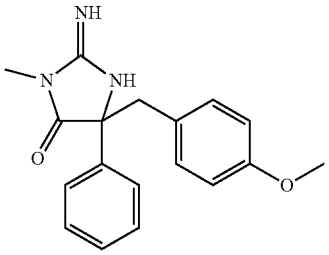
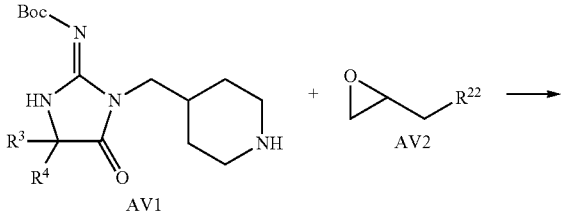
#	Structure	MW	Obs. m/e
447		285	286
448		285	286
449		309	310
450		309	310

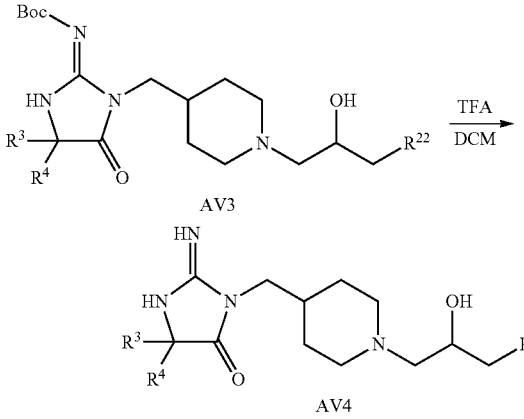
Method AV



AV1

AV2

-continued



AV3

AV4

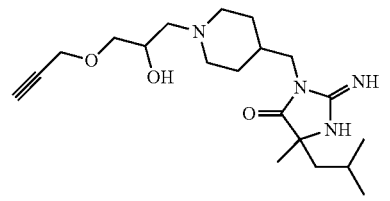
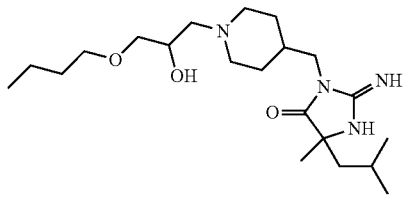
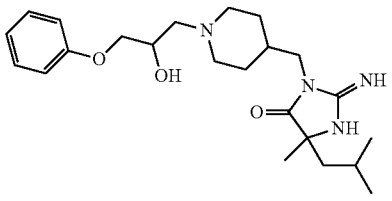
Method AV, Step 1:

In a microwave tube, AV1 (R^3=Me, R^4=Bu-i) (0.0012 g) and AV2 (R^{22}=OPh) (0.0059 nil) in isopropanol (2 ml) was placed in a microwave at 125° C. for 5 min. The reaction mixture was concentrated in vacuo to give AV3 (R^3=Me, R^4=i-Bu, R^{22}=OPh).

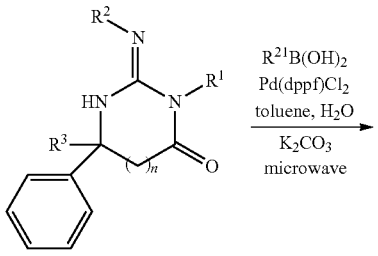
Method AV, Step 2:

AV3 (R^3=Me, R^4=i-Bu, R^{22}=OPh) in CH_2Cl_2 (1 ml) and TFA (1 ml) was shaken for 2 h and the concentrated in vacuo and purified on Prep LCMS to afford AV4 (R^3=Me, R^4=i-Bu, R^{22}=OPh).

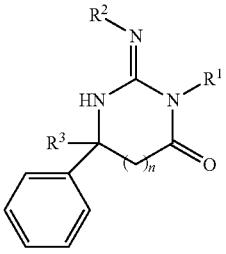
The following compounds were synthesized in a similar fashion.

#	Structure	MW	Obs. m/e
451		378	379
452		396	397
453		416	417

Method AW



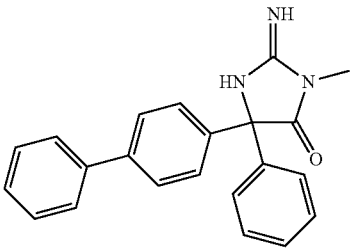
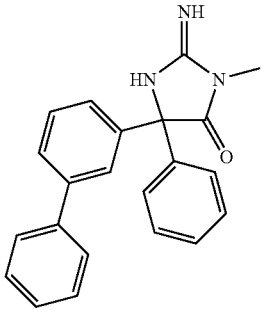
AW1



AW2

Method similar to Method U was used for this transformation. The following compounds were generated using similar methods.

The following compounds were synthesized in a similar fashion:

#	Structure	MW	Obs. m/e
454		341	342
455		341	342

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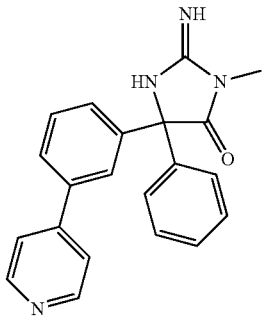
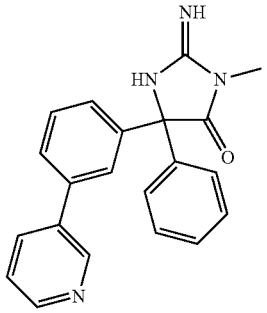
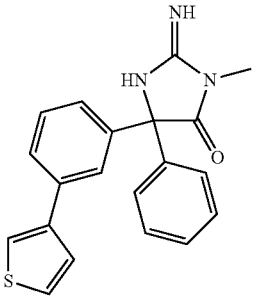
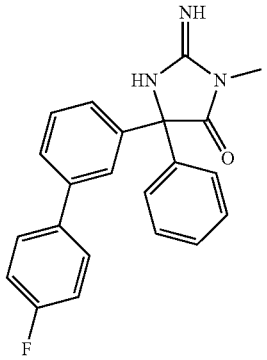
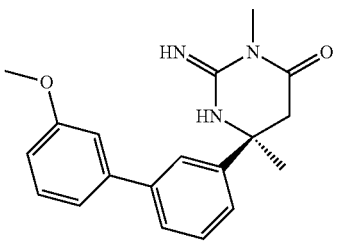
#	Structure	MW	Obs. m/e
456		342	343
457		342	343
458		347	348
459		359	360
460		323	324

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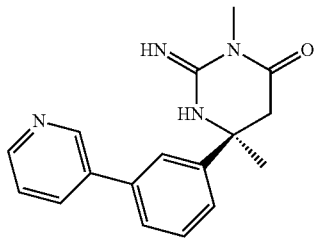
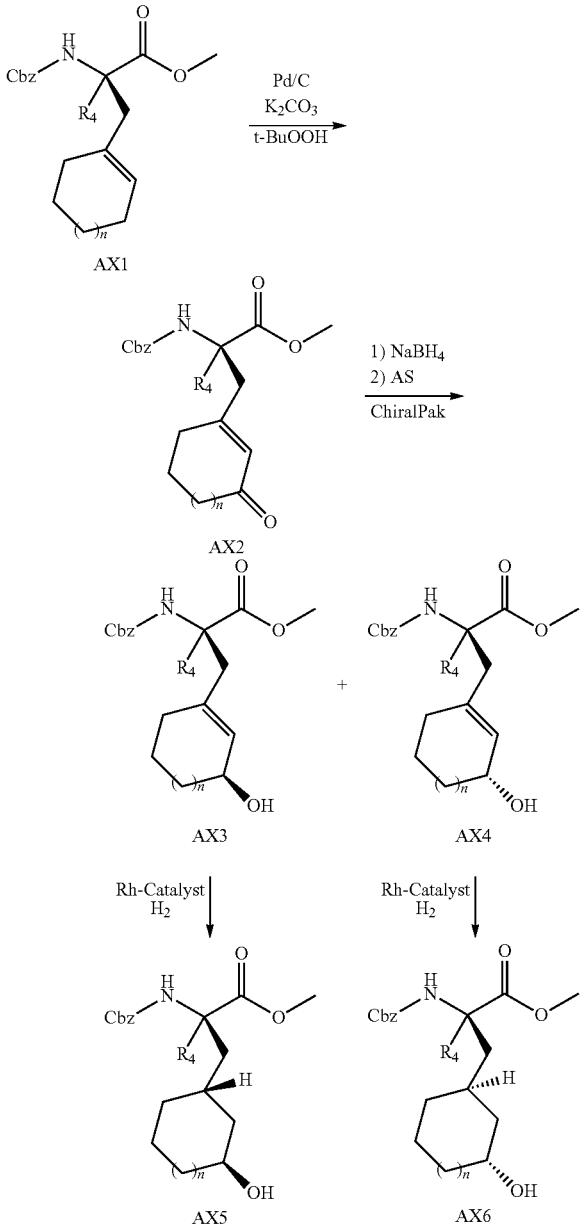
#	Structure	MW	Obs. m/e
461		294	295

Method AX



Method AX, Step 1.

A literature procedure was adapted. (J-Q Yu and E. J. Corey, *Organic Letters*, 2002, 4, 2727-2730).

To a 400 ml DCM solution of AX1 (n=1, R^4=phenethyl) (52 grams) in a ice bath was added 5 g of Pd/C (5% w/w), 50 g of potassium carbonate and 100 ml of anhydrous t-BuOOH. The mixture was stirred in air for overnight before it was diluted with DCM and washed with water. The residue after removal of organic solvent and drying was chromatographed using ethylacetate/hexane to give 25 g of AX2 (n=1, R^4=phenethyl).

Method AX, Step 2.

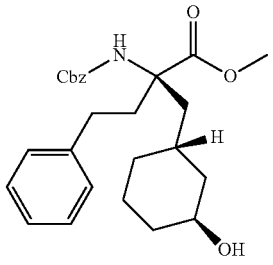
A solution of AX2 (4.5 g, n=1, R^4=phenethyl) in MeOH (50 ml) was treated with 0.4 g of Sodium borohydride and the reaction was stirred for 30 min before the solvent was removed and residue chromatographed to give a mixture of AX3 (n=1, R^4=phenethyl) and AX4 (n=1, R^4=phenethyl) which was separated using an AS chiralpak column eluted with 8% IPA in Hexane (0.05% DEA) to give 2.1 g of AX3 (n=1, R^4=phenethyl) as the first fraction and 2.2 g of AX4 (n=1, R^4=phenethyl) as the second fraction.

Method AX, Step 3.

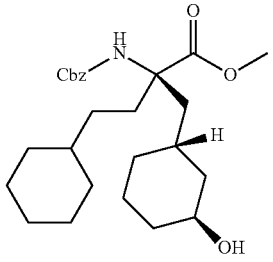
A 100 ml methanolic solution of AX4 (n=1, R^4=phenethyl) (2.2 g) and 1,1'-bis(di-i-propylphosphino)ferrocene (1,5-cyclooctadiene)rhodium (I) tetrafluoroborate (0.4 g, 0.57 mmol) was hydrogenated at 55 psi overnight. The reaction was concentrated, and the brown oil was purified by silica gel chromatography to yield AX6 (n=1, R^4=phenethyl) (1.7 g).

The following compounds were generated using similar method.

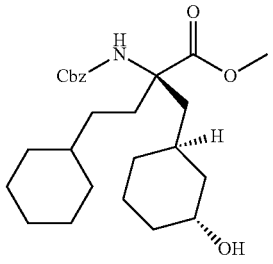
AX7



AX8



AX9



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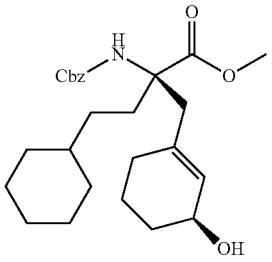
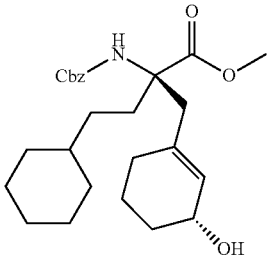
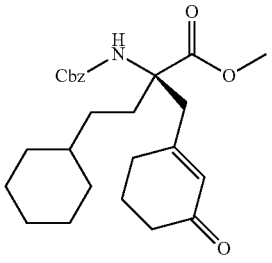
AX10



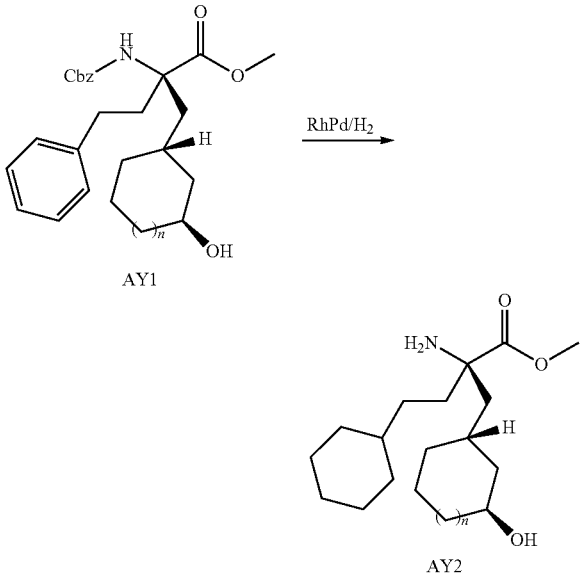
AX11



AX12



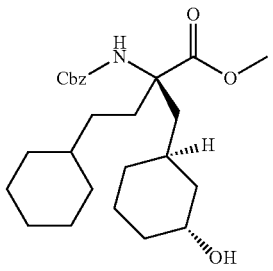
Method AY



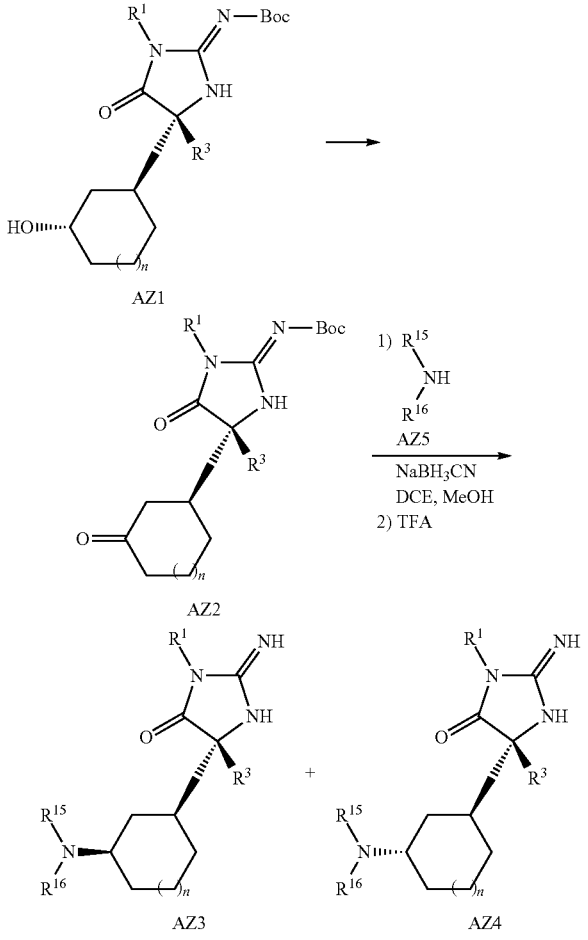
A solution of AY1 (n=1; 1.5 g, 3.4 mmol), 5% Rh/C (1.5 g), 5% Pd/C (0.5 g) in AcOH (30 mL) was shaken in a Parr apparatus at 55 psi for 18 hours. The vessel was flushed with N_2, and the reaction was filtered through a pad of celite. After concentration AY2 was obtained which was carried on without purification. MS m/e: 312.0 (M+H).

AY3 was generated using similar method.

AY3



Method AZ



Method AZ, Step 1

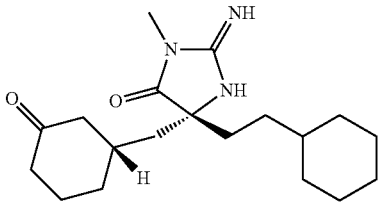
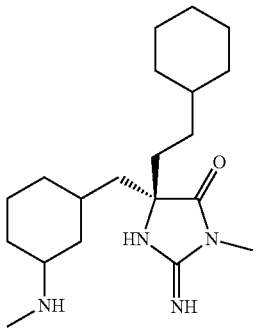
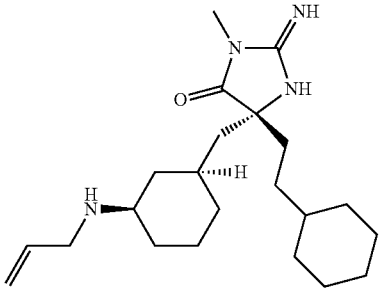
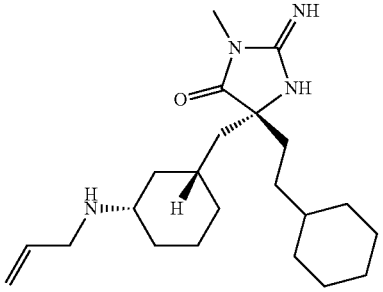
To a solution of AZ1 (n=1, R^1=Me, R^3=2-cyclohexylethyl) (0.441 g, 1.01 mmol), generated from AY2 using Method C and Method H Step 3, in DCM was added Dess-Martin Periodinane (0.880 g, 2.07 mmol). The reaction was stirred for 3 hours at room temperature. The reaction was quenched with H_2O and diluted with EtOAc. After removal of the organic phase, the aqueous layer was extracted with EtOAc (3×). The

combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (0-100% EtOAc/hexanes) to yield AZ2 (n=1, R^1=Me, R^3=2-cyclohexylethyl) (0.408 g, 0.94 mmol, 93% yield). MS m/e: 434.1 (M+H).

Method AZ Step 2:

To a solution of AZ2 (n=1, R^1=Me, R^3=2-cyclohexylethyl) (0.011 g, 0.025 mmol) and AZ5 (R^{15}=H and R^{16}=m-pyridylmethyl) (0.0067 mL, 0.066 mmol) in DCE (1.8 mL) and MeOH (0.2 mL) was added AcOH (4 drops) and MP-cyanoborohydride resin (0.095 g, 2.42 mmol/g). The reaction was agitated for 40 hours at room temperature. The reaction was treated with 7N NH_3/MeOH, and solution was filtered. After concentration, the residue was purified by silica gel HPLC (0-4% [(5% 7N NH_3/MeOH)/MeOH]/(50% DCM/hexanes) to furnish fraction 1 and fraction 2 which, after removal of solvent, were treated with 20% TFA in DCM for 3 h at r.t. to give AZ4 (n=1, R^1=Me, R^3=2-cyclohexylethyl, R^{15}=H and R^{16}=m-pyridylmethyl) (0.005 g, 0.009 mmol) and the AZ3 (n=1, R^1=Me, R^3=2-cyclohexylethyl, R^{15}=H and R^{16}=m-pyridylmethyl) (0.012 g, 0.022 mmol) respectively.

The following compounds were generated using similar methods:

#	Structure	MW	Obs. m/e
462		333	334
463		348	349
464		374	375
465		374	375

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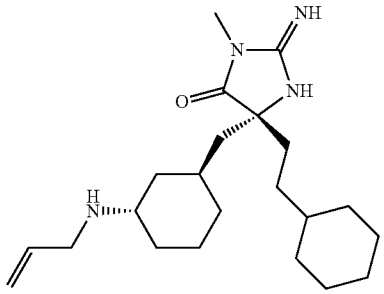
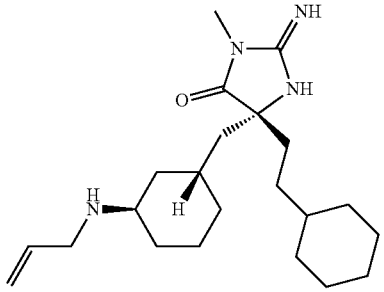
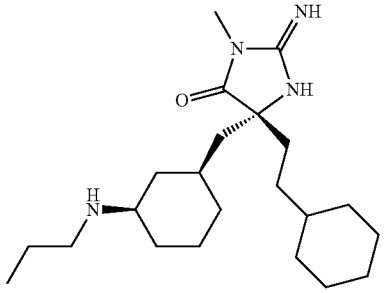
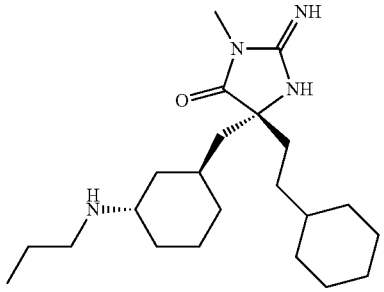
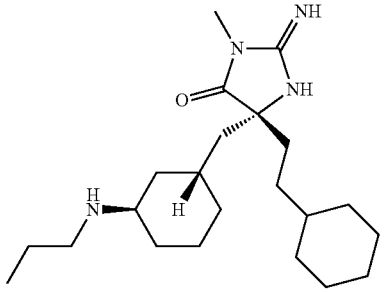
#	Structure	MW	Obs. m/e
466		374	375
467		374	375
468		376	377
469		376	377
470		376	377

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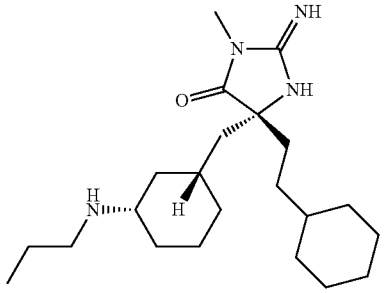
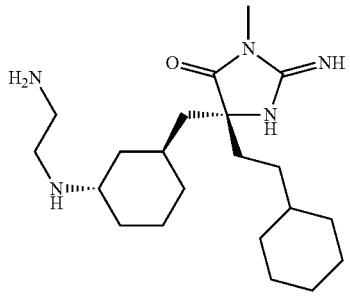
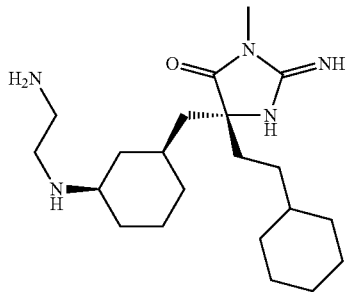
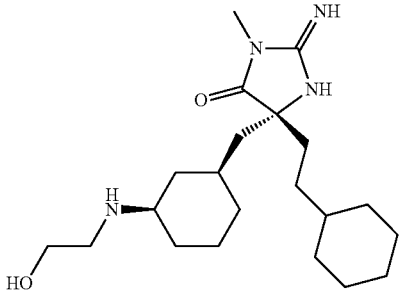
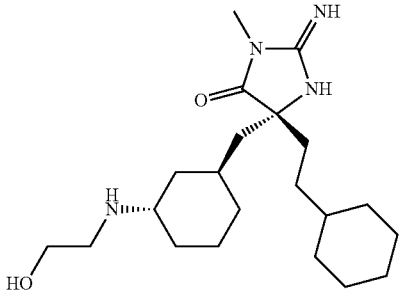
#	Structure	MW	Obs. m/e
471		376	377
472		377	378
473		377	378
474		378	379
475		378	379

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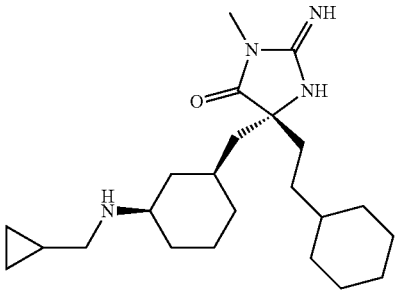
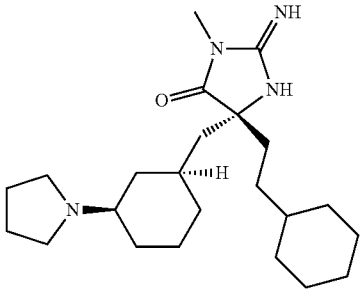
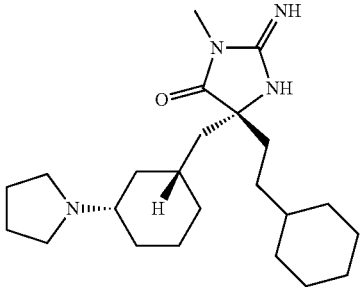
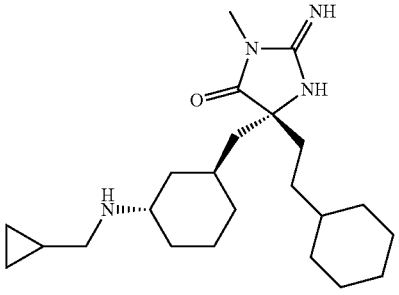
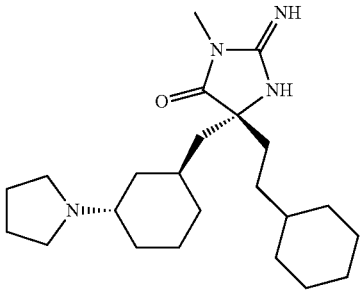
#	Structure	MW	Obs. m/e
476		388	389
477		388	389
478		388	389
479		388	389
480		388	389

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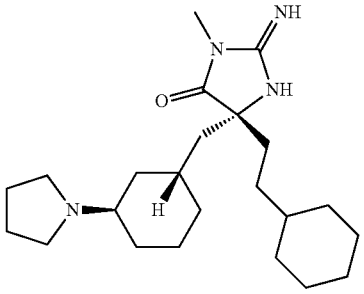
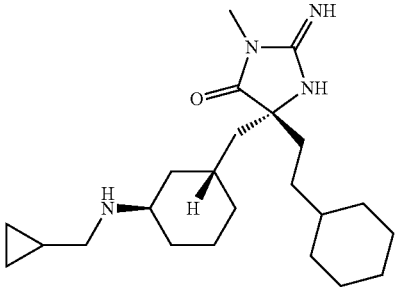
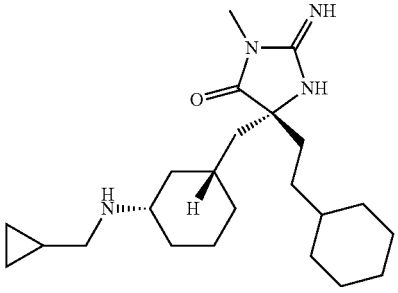
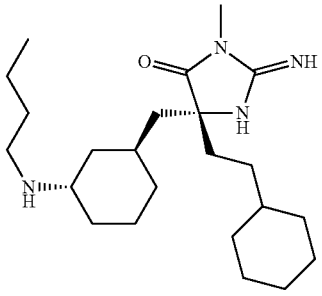
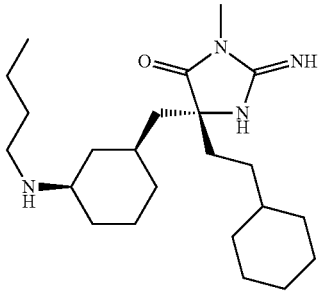
#	Structure	MW	Obs. m/e
481		388	389
482		388	389
483		388	389
484		390	391
485		390	391

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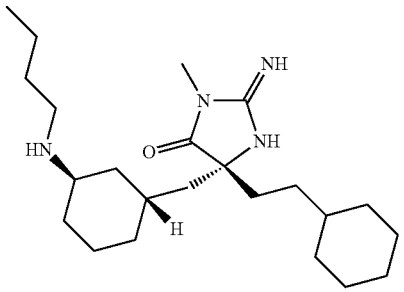
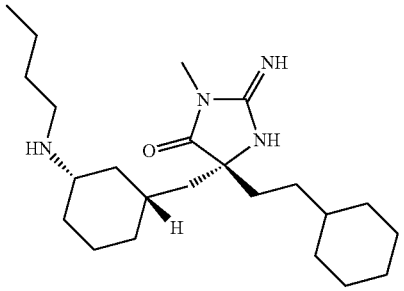
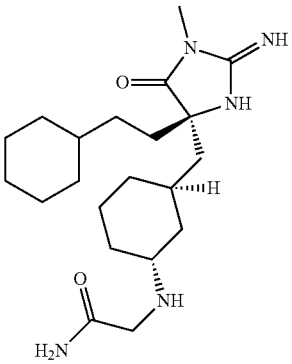
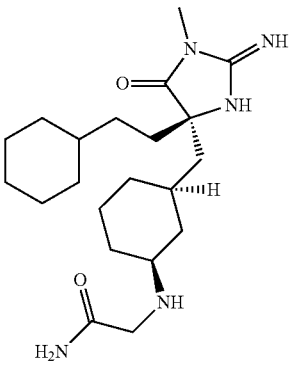
#	Structure	MW	Obs. m/e
486		390	391
487		390	391
488		391	392
489		391	392

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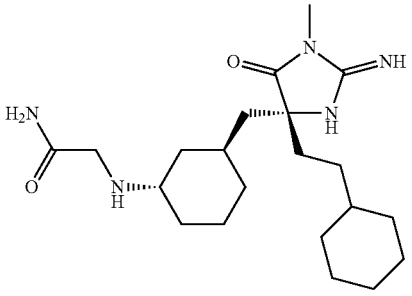
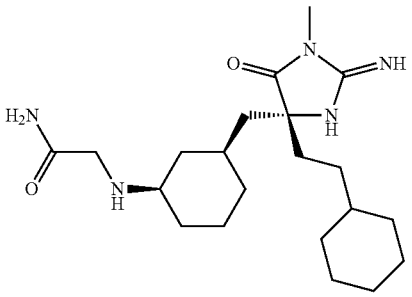
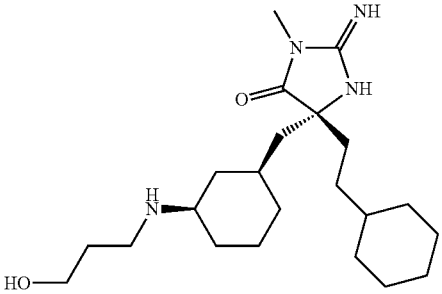
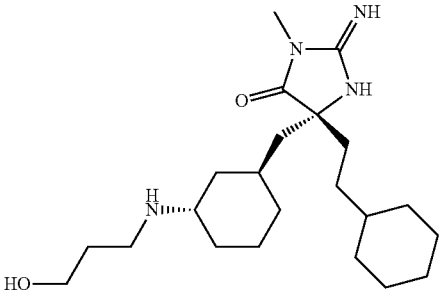
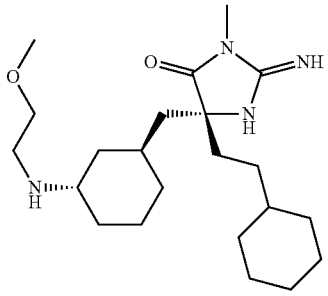
#	Structure	MW	Obs. m/e
490		391	392
491		391	392
492		392	393
493		392	393
494		392	393

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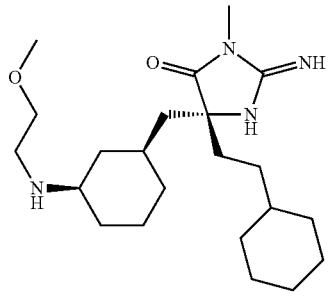
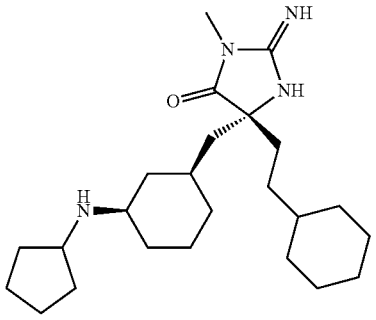
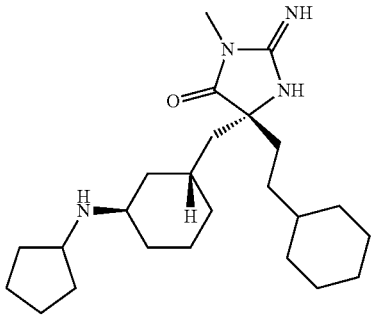
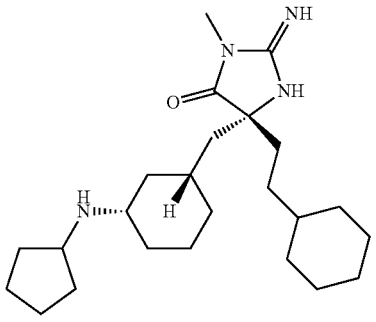
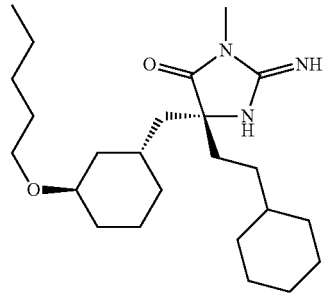
#	Structure	MW	Obs. m/e
495		392	393
496		402	403
497		402	403
498		402	403
499		405	406

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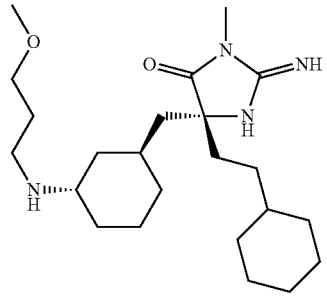
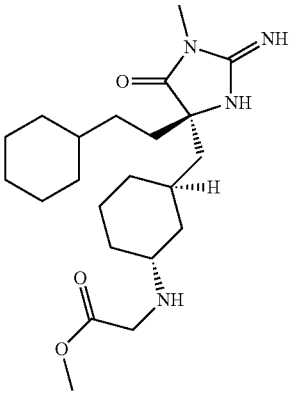
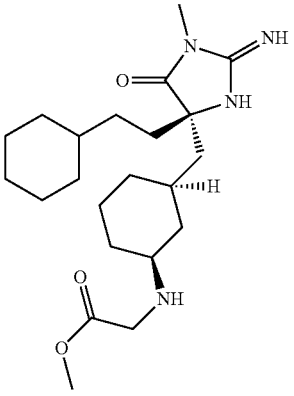
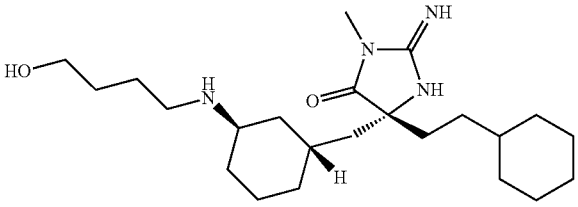
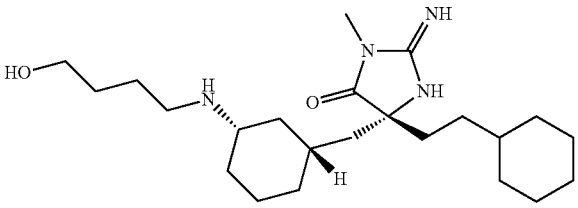
#	Structure	MW	Obs. m/e
500		406	407
501		406	407
502		406	407
503		406	407
504		406	407

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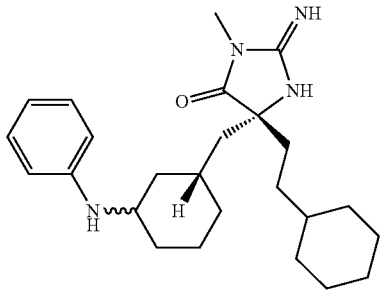
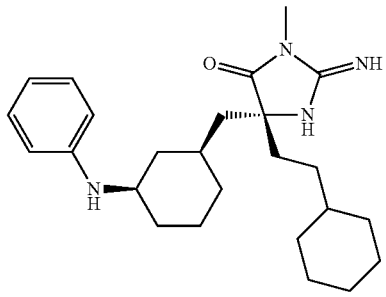
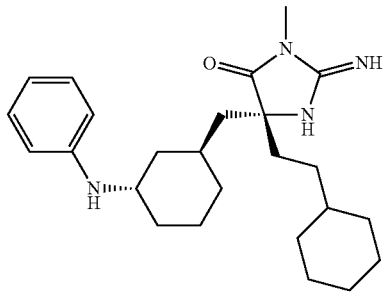
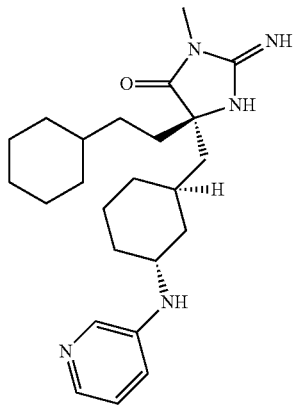
#	Structure	MW	Obs. m/e
505		410	411
506		410	411
507		410	411
508		411	412

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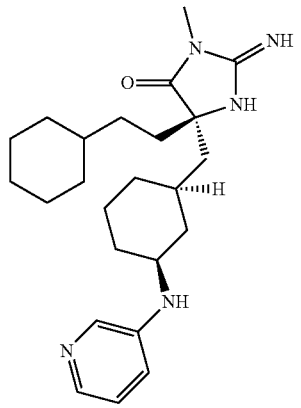
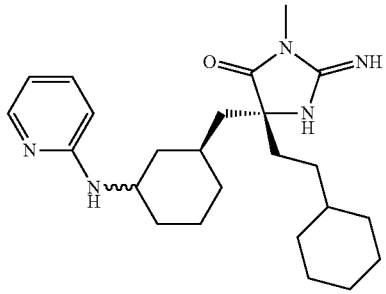
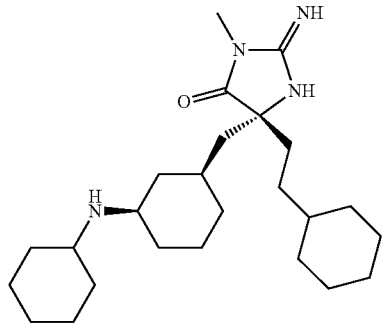
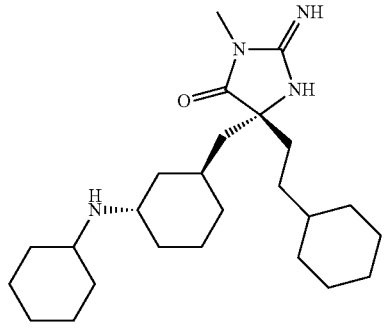
#	Structure	MW	Obs. m/e
509		411	412
510		411	412
511		416	417
512		416	417

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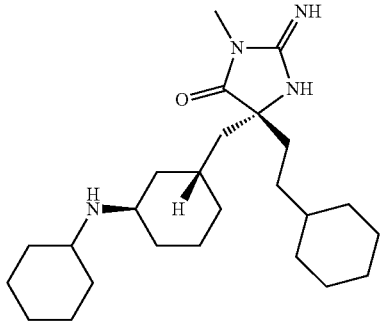
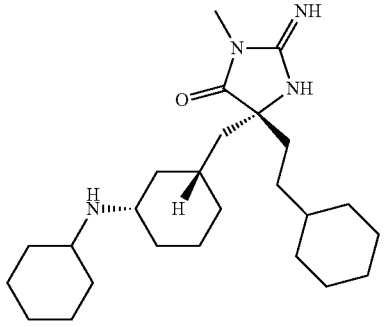
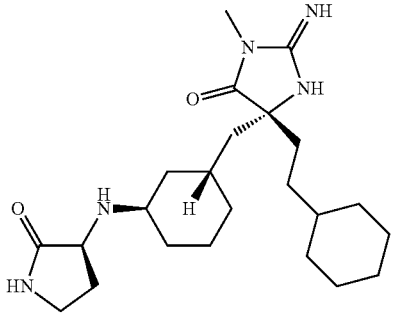
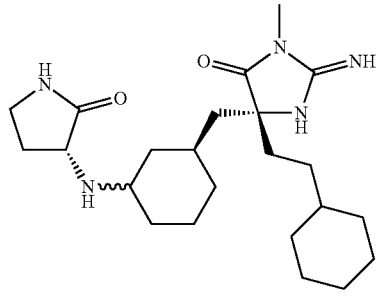
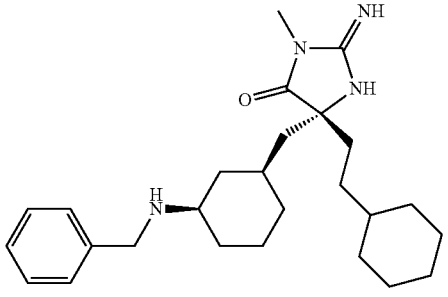
#	Structure	MW	Obs. m/e
513		416	417
514		416	417
515		417	418
516		417	418
517		424	425

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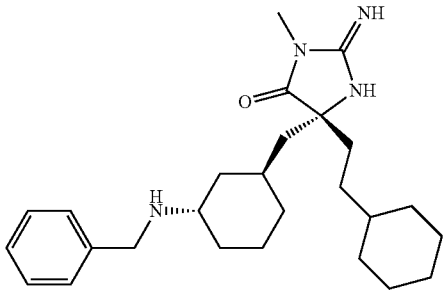
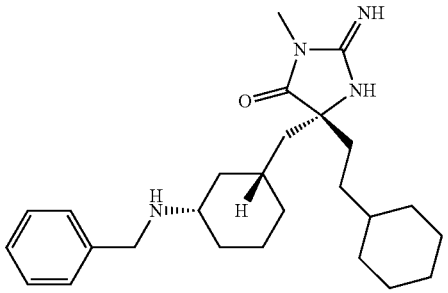
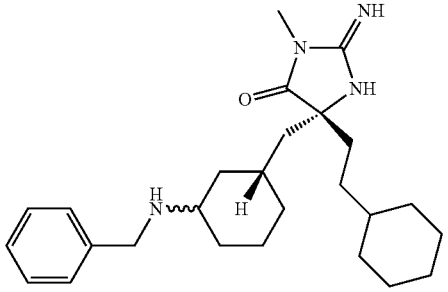
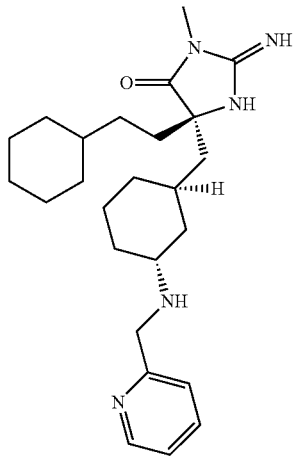
518		424	425
519		424	425
520		424	425
521		425	426

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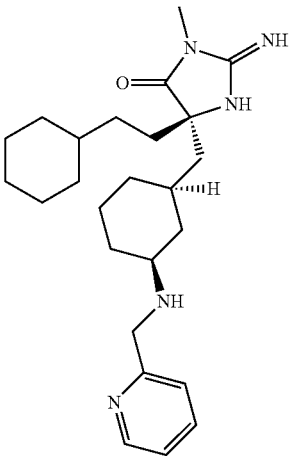
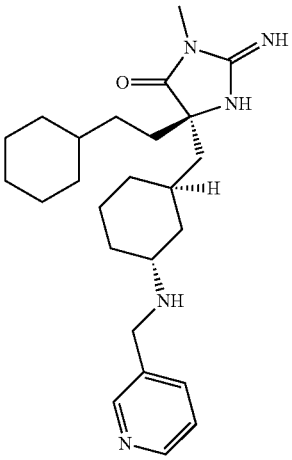
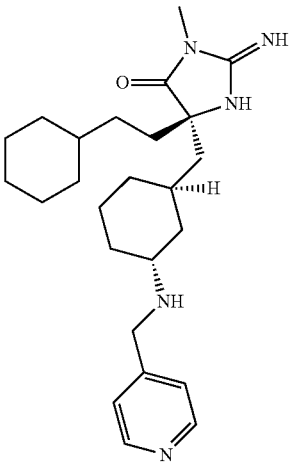
#	Structure	MW	Obs. m/e
522		425	426
523		425	426
524		425	426

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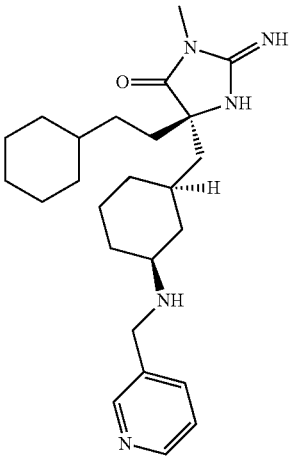
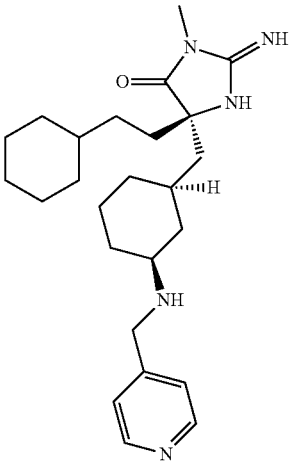
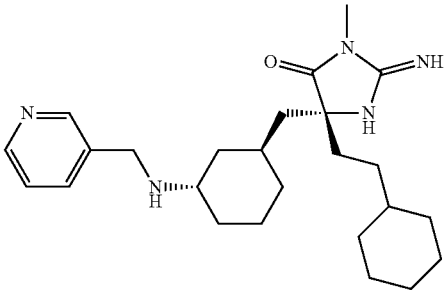
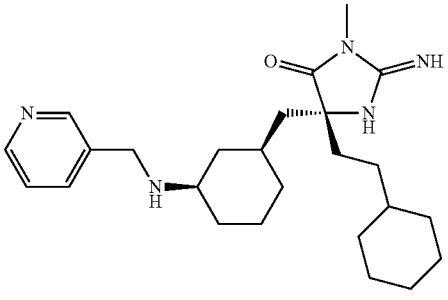
#	Structure	MW	Obs. m/e
525		425	426
526		425	426
527		425	426
528		425	426

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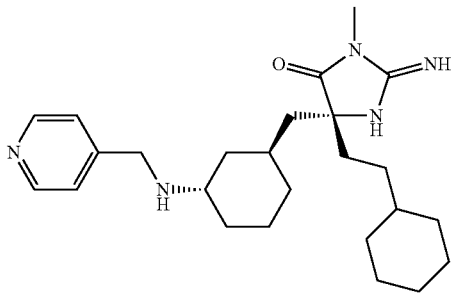
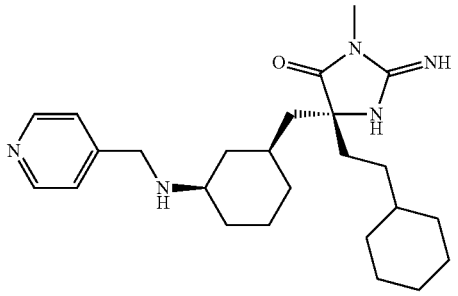
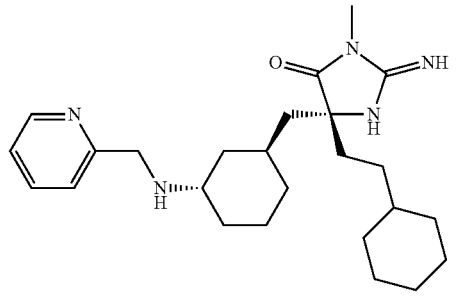
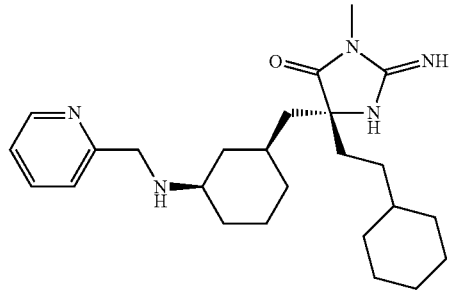
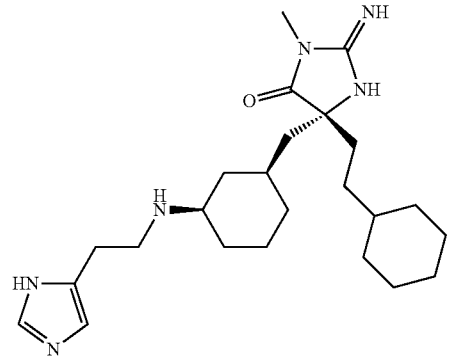
#	Structure	MW	Obs. m/e
529		425	426
530		425	426
531		425	426
532		425	426
533		428	429

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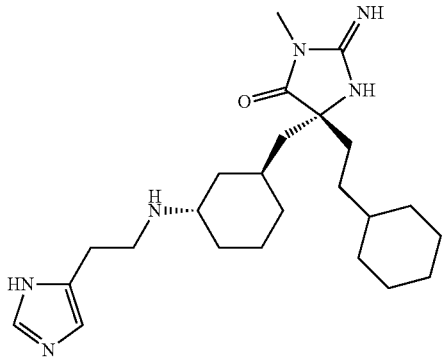
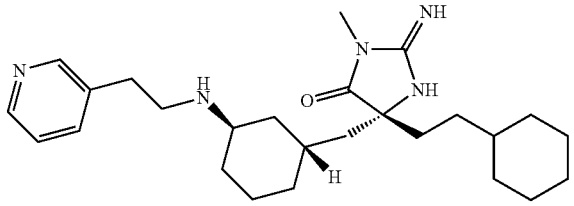
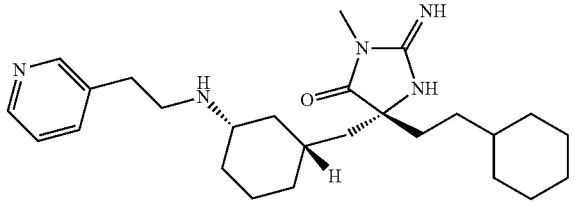
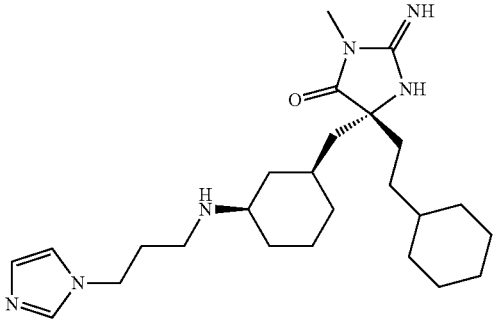
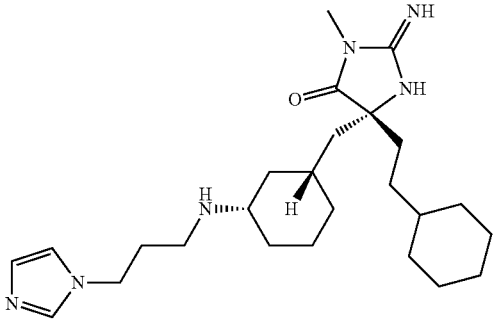
#	Structure	MW	Obs. m/e
534		428	429
535		439	440
536		439	440
537		442	443
538		442	443

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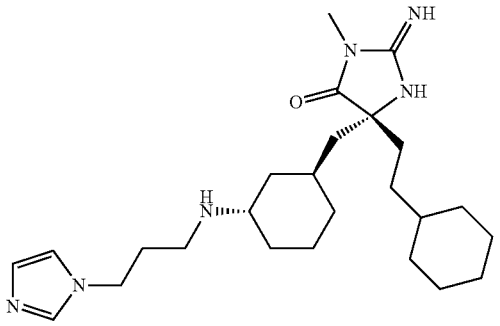
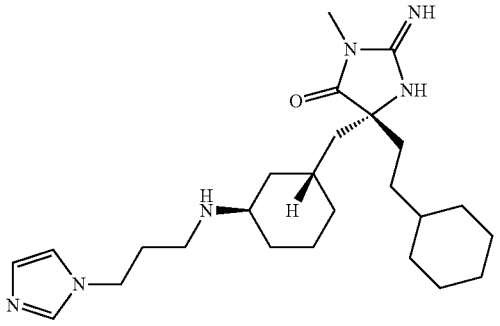
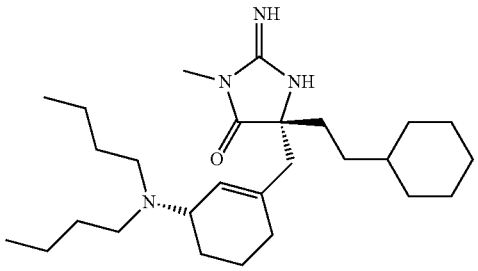
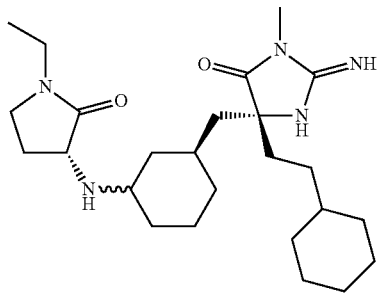
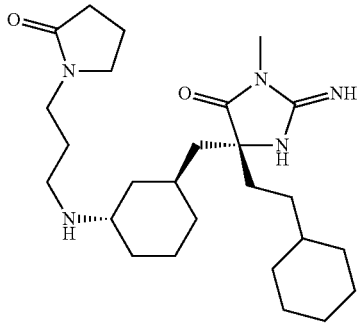
#	Structure	MW	Obs. m/e
539		442	443
540		442	443
541		444	445
542		445	446
543		459	460

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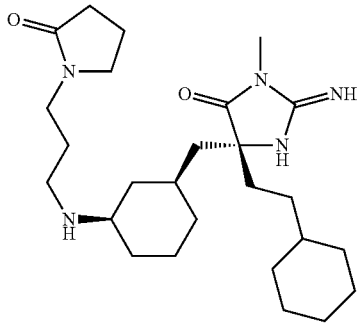
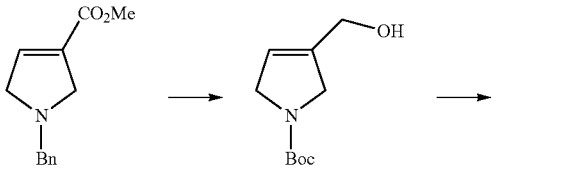
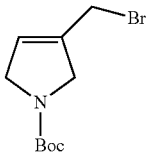
#	Structure	MW	Obs. m/e
544		459	460

Method BA



BA1 BA2



BA3

Method BA, Step 1:

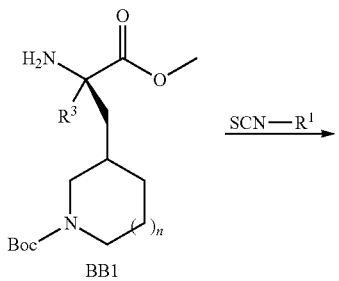
BA1, prepared according to a literature procedure (Terao, Y; Kotaki, H; Imai, N and Achiwa K. Chemical and Pharmaceutical Bulletin, 33 (7), 1985, 2762-2766) was converted to BA2 using a procedure described by Coldham, I; Crapnell, K. M; Fernandez, J-C; Moseley J. D. and Rabot, R (*Journal of Organic Chemistry*, 67 (17), 2002, 6185-6187).

^{1}H NMR ($CDCl_3$) for BA2: 1.42 (s, 9H), 4.06 (d, 4H), 4.09 (s, 1H), 4.18 (s, 2H), 5.62 (d, 1H).

Method BA, Step 2:

BA3 was generated from BA2 using a literature procedure described by Winkler J. D.; Axten J.; Hammach A. H.; Kwak, Y-S; Lengweiler, U.; Lucero, M. J.; Houk, K. N. (Tetrahedron, 54 1998, 7045-7056). Analytical data for compound BA3: MS m/e: 262.1, 264.1 (M+H). ^{1}H NMR ($CDCl_3$) 1.43 (s, 9H), 3.98 (s, 2H), 4.11 (d, 4H), 5.78 (d, 1H).

Method BB



BB1

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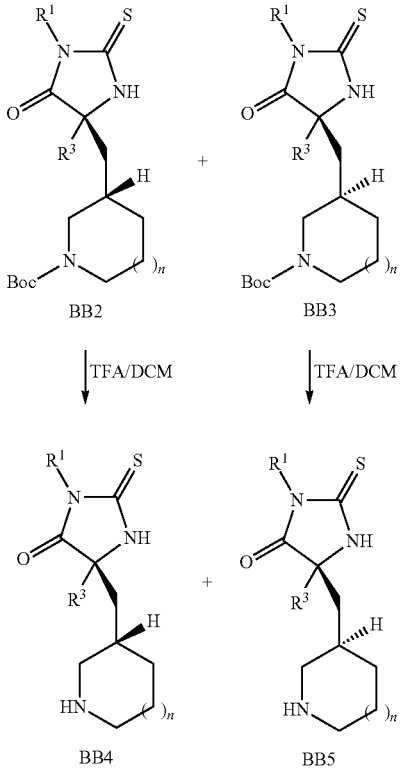


BB2 BB3

BB4 BB5

Method BB, Step 1;

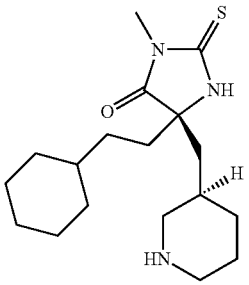
Compound BB1 (n=1, R^1=Me, R^3=cyclohexylethyl) was converted to BB2 (n=1, R^1=Me, R^3=cyclohexylethyl) and BB3 (n=1, R^1=Me, R^3=cyclohexylethyl) which were separated via a silica gel column eluted with EtOAc in Hexane (0-15%).

Method BB, Step 2;

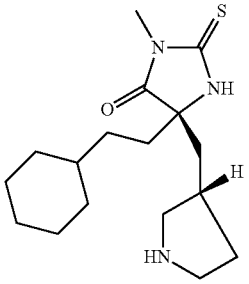
Compound BB4 (n=1, R^1=Me, R^3=cyclohexylethyl) was generated from BB2 (n=1, R^1=Me, R^3=cyclohexylethyl) using 20% TFA in DCM.

The following compounds were generated using similar method:

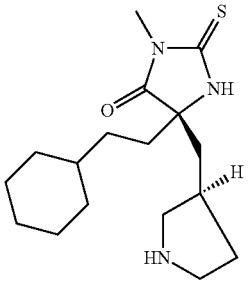
BB5



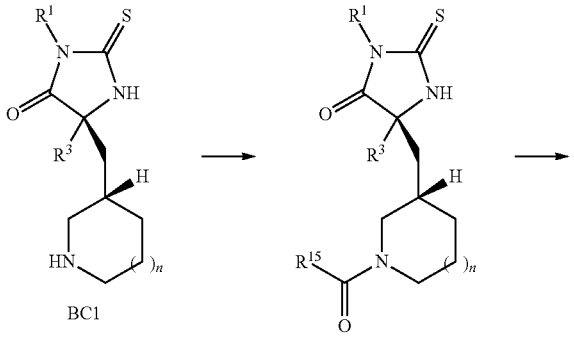
BB6



BB7

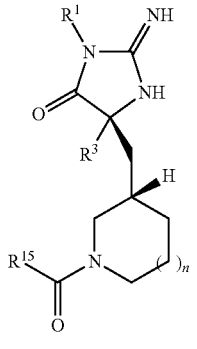


Method BC



BC1

BC2



BC3

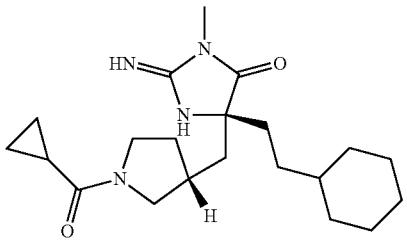
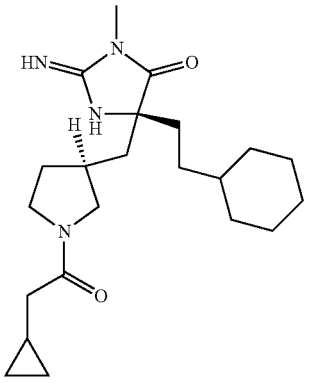
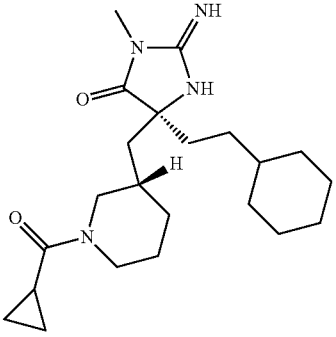
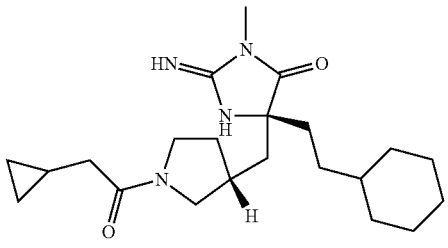
Method BC, Step 1;

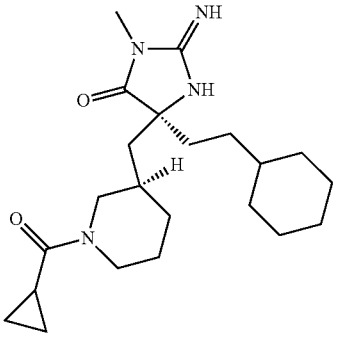
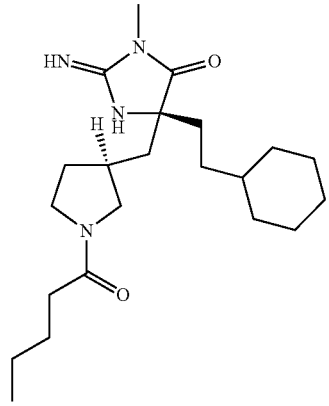
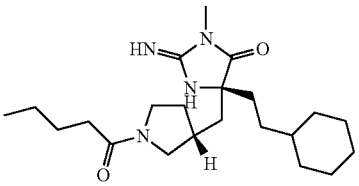
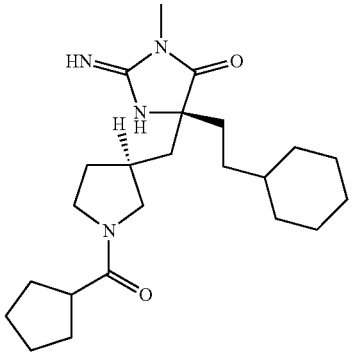
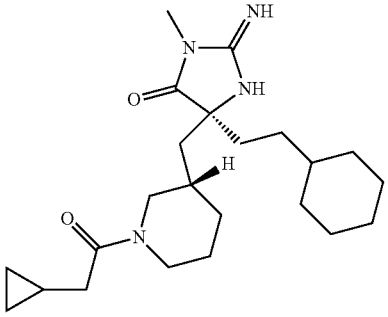
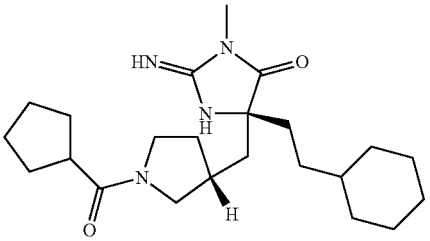
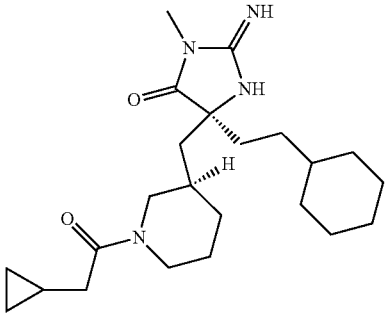
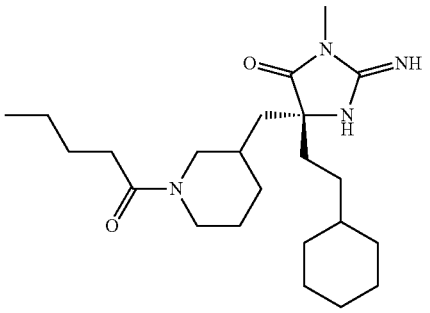
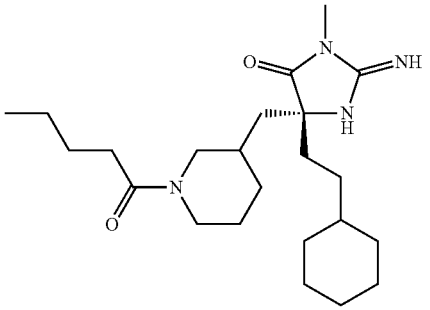
Compound BC2 (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=m-Pyridyl) was obtained from BC1 (n=1, R^2=Me, R^3=cyclohexylethyl) using method L step 2.

Method BC, Step 2;

Compound BC3 (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=m-Pyridyl) was obtained from BC2 (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=m-Pyridyl) using method L step 3.

The following compounds were generated using a similar method:

#	Structure	MW	Obs. m/e
552		374	375
553		388	389
554		388	389
555		388	389

#	Structure	MW	Obs. m/e
556		388	389
557		390	391
558		390	391
559		402	403
560		402	403
561		402	403
562		402	403
563		404	405
564		404	405

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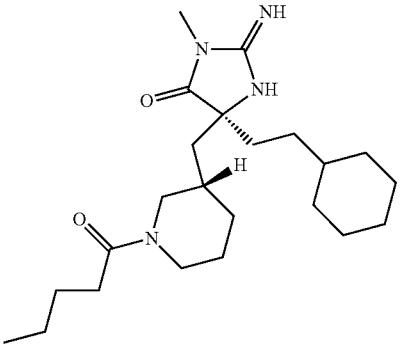
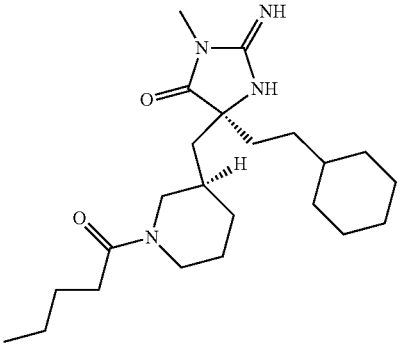
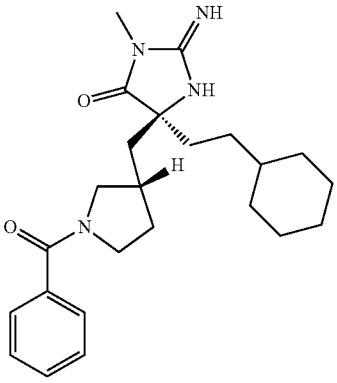
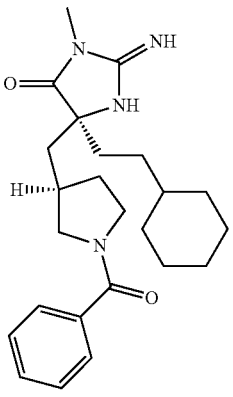
#	Structure	MW	Obs. m/e
565		404	405
566		404	405
567		410	411
568		410	411

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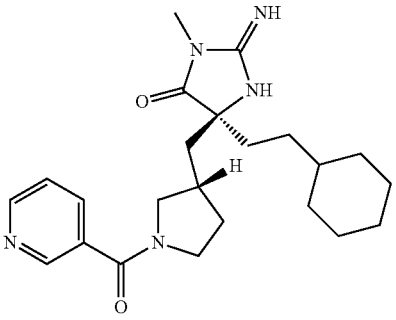
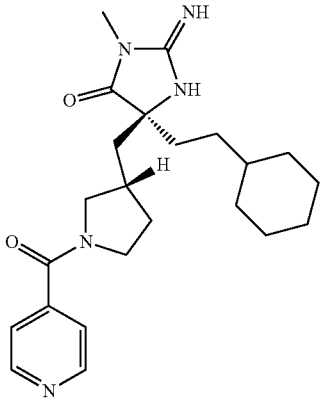
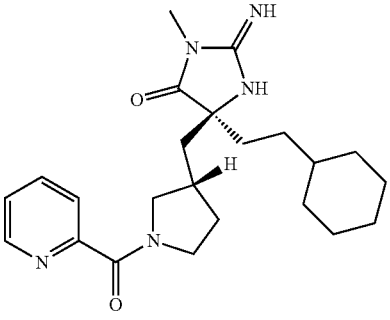
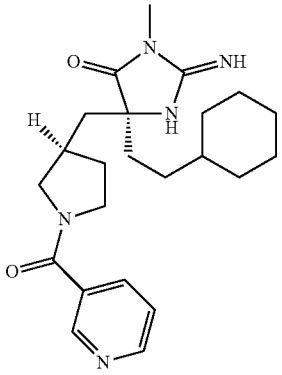
#	Structure	MW	Obs. m/e
569		411	412
570		411	412
571		411	412
572		411	412

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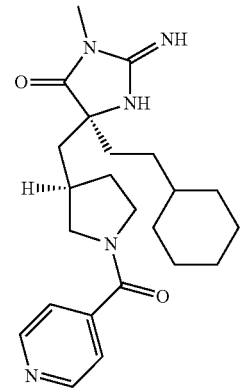
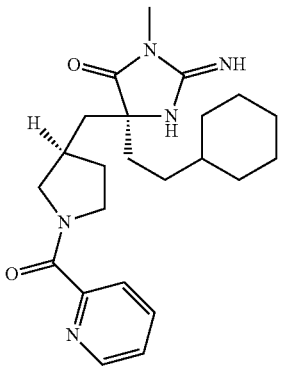
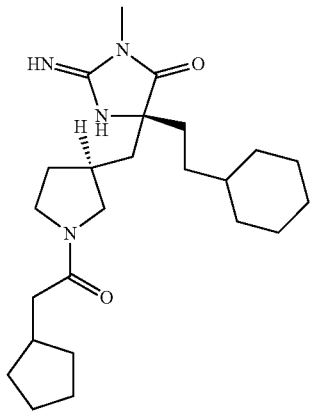
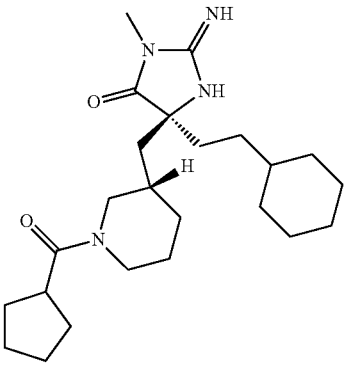
#	Structure	MW	Obs. m/e
573		411	412
574		411	412
575		416	417
576		416	417

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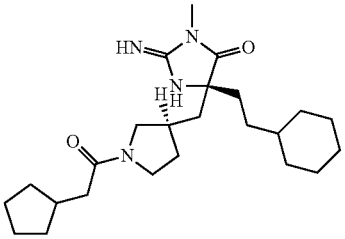
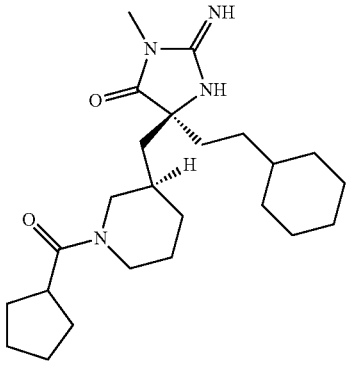
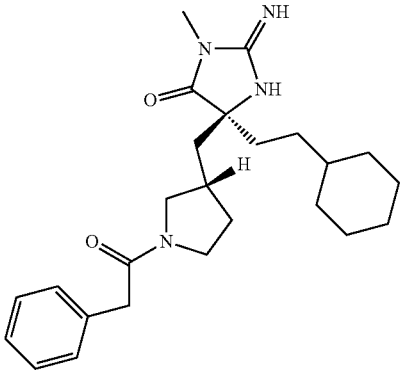
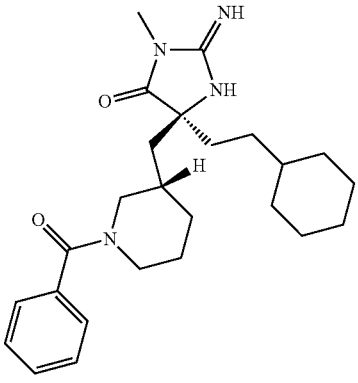
#	Structure	MW	Obs. m/e
577		416	417
578		416	417
579		424	425
580		424	425

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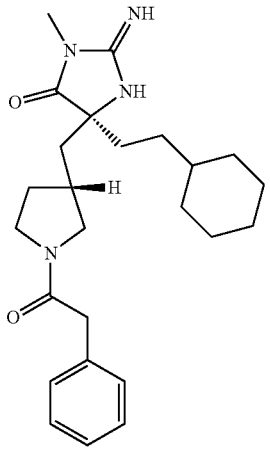
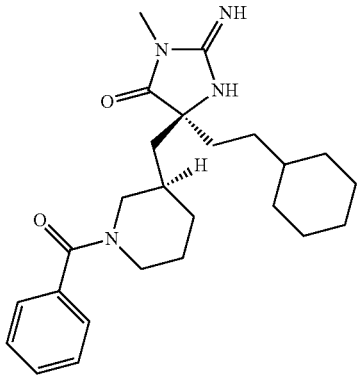
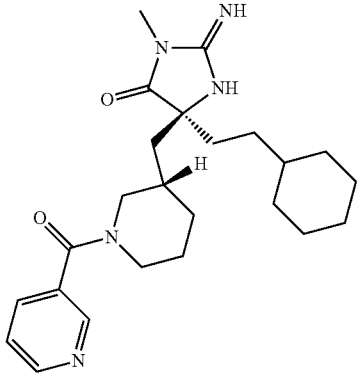
#	Structure	MW	Obs. m/e
581		424	425
582		424	425
583		425	426

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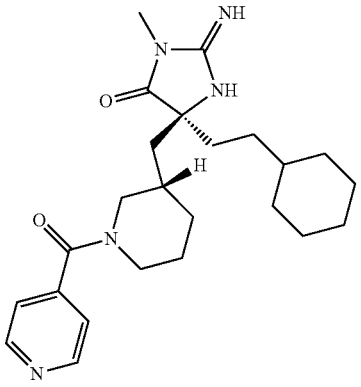
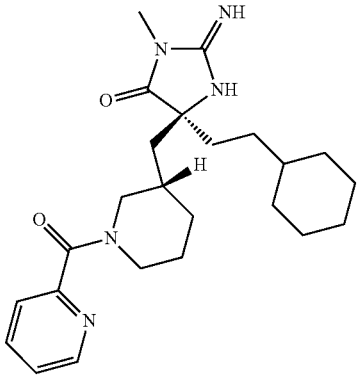
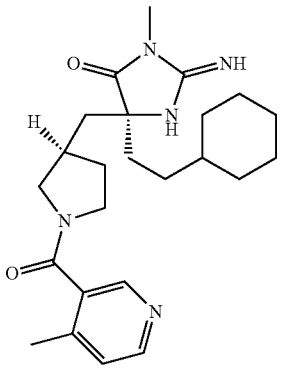
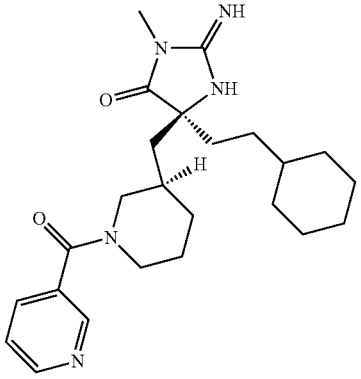
#	Structure	MW	Obs. m/e
584		425	426
585		425	426
586		425	426
587		425	426

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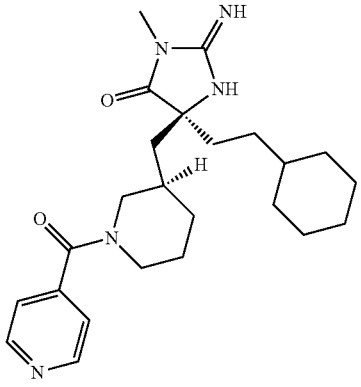
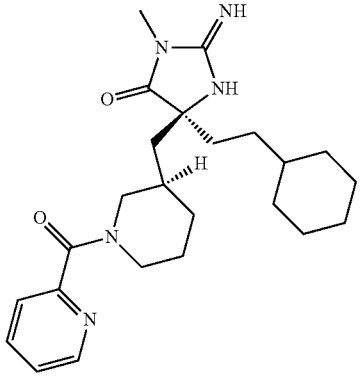
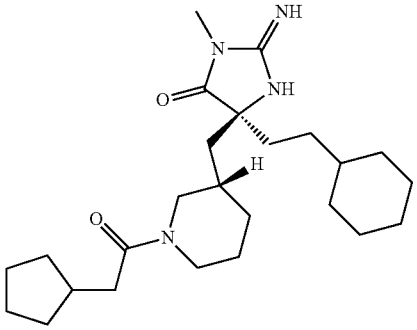
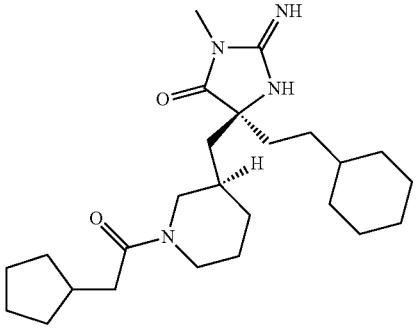
#	Structure	MW	Obs. m/e
588		425	426
589		425	426
590		430	431
591		430	431

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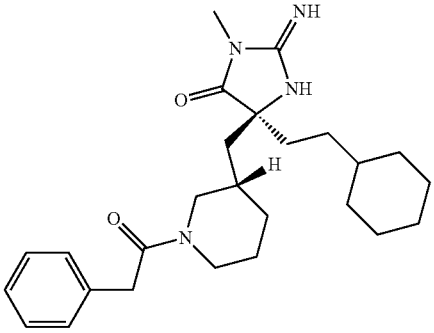
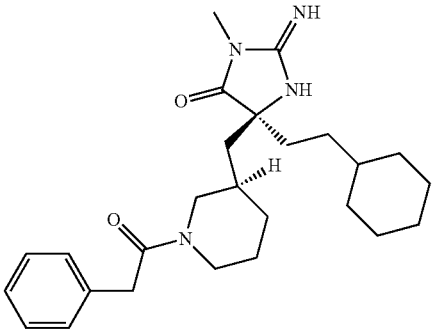
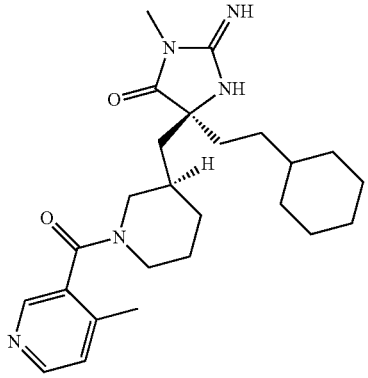
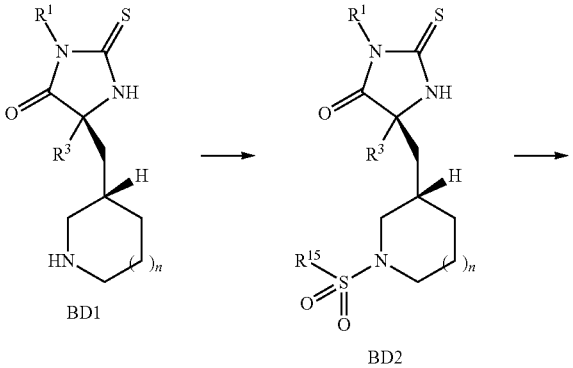
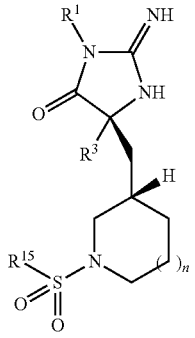
#	Structure	MW	Obs. m/e
592		438	439
593		438	439
594		439	440

Method BD





BD3

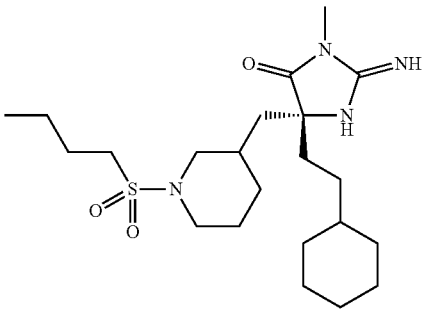
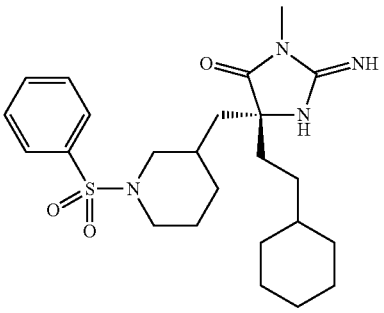
Method BD, Step 1;

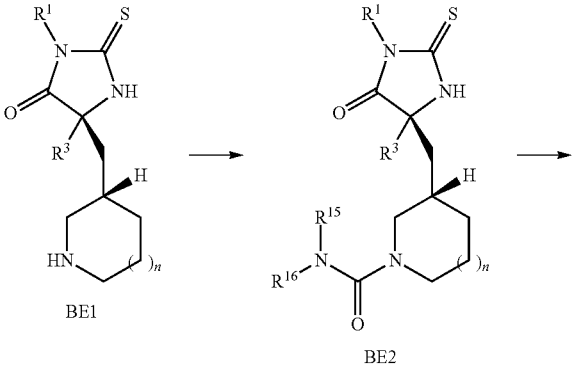
Compound BD2 (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=Ph) was obtained from BD1 (n=1, R^2=Me, R^3=cyclohexylethyl) using Method N, Step 1.

Method BD, Step 2;

Compound BD3 (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=Ph) was obtained from BD2 (n=1, R^1=Me, R^3=cyclohexylethyl and R^{15}=m-Pyridyl) using Method N, Step 2.

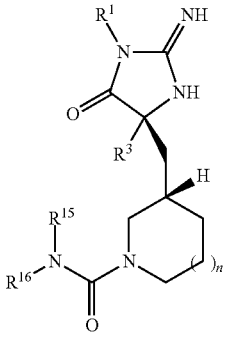
The following compounds were generated using a similar method:

#	Structure	MW	Obs. m/e
595		440	441
596		460	461



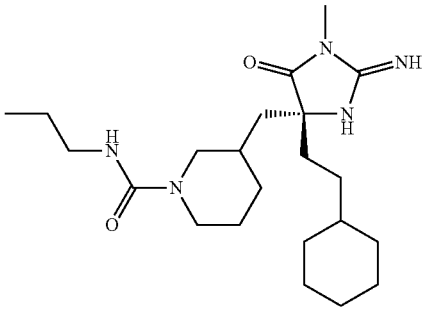
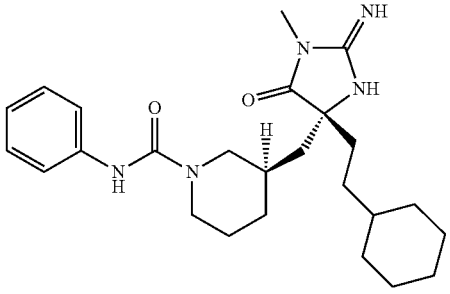
BE1

BE2

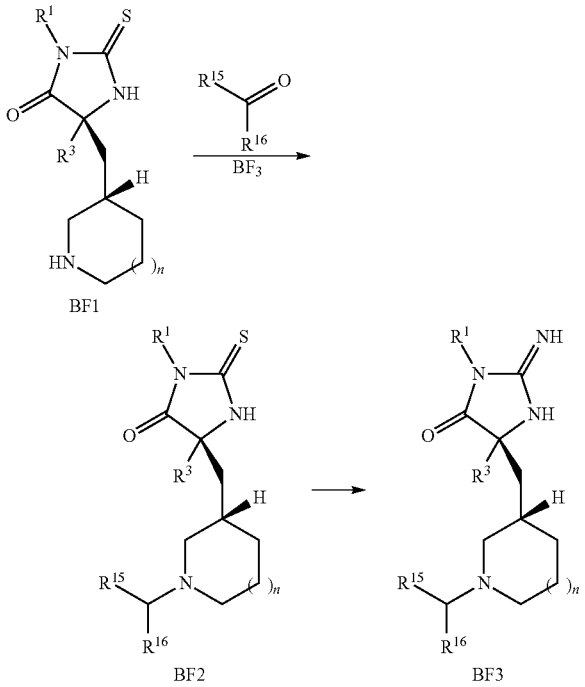


BE3

Method similar to Method M was adapted for these transformations. The following compounds were generated similar methods.

#	Structure	MW	Obs. m/e
597		405	406
598		439	440

Method BF



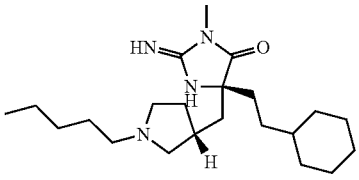
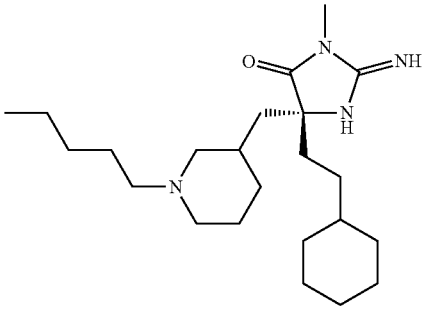
Method BF, Step 1:

Method similar to Method T, Step 1 was used for the synthesis of BF2 (n=1, R^1=Me and R^3=phenethyl, R^{15}=H and R^{16}=n-propyl).

Method BF, Step 2:

Method similar to method L Step 3 was adapted for this transformation.

The following compounds were generated using similar methods.

#	Structure	MW	Obs. m/e
599		376	377
600		390	391

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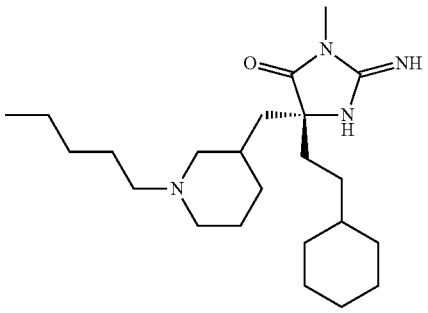
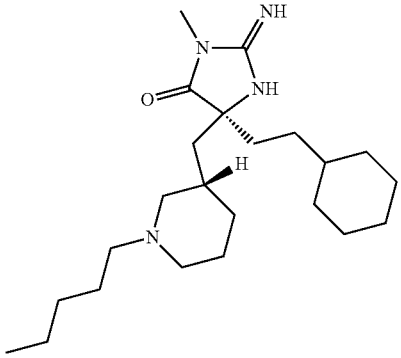
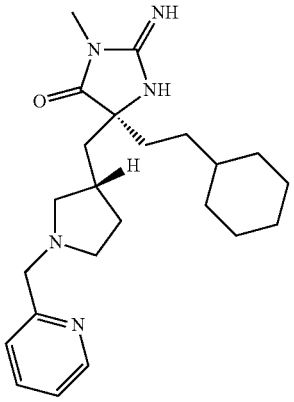
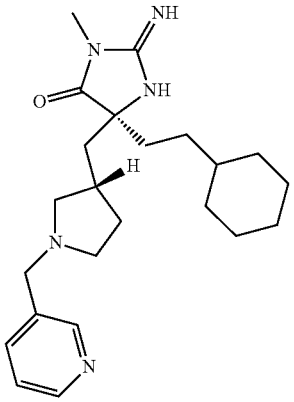
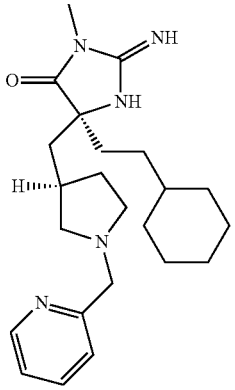
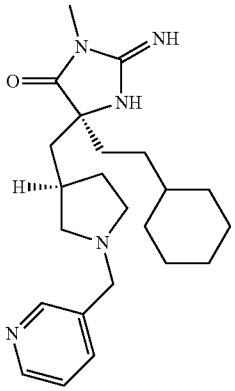
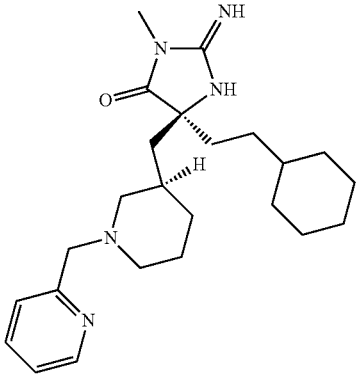
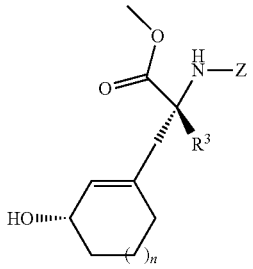
#	Structure	MW	Obs. m/e
601		390	391
602		390	391
603		397	398
604		397	398

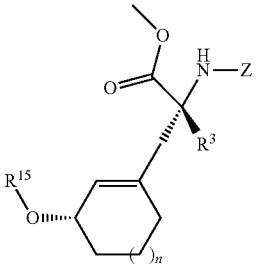
-continued

#	Structure	MW	Obs. m/e
605		397	398
606		397	398
607		411	412

Method BG



BG1



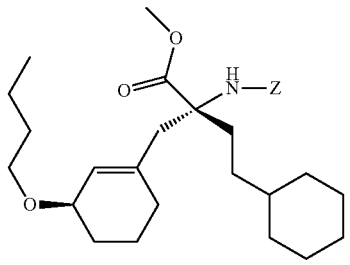
BG 2

Method BG:

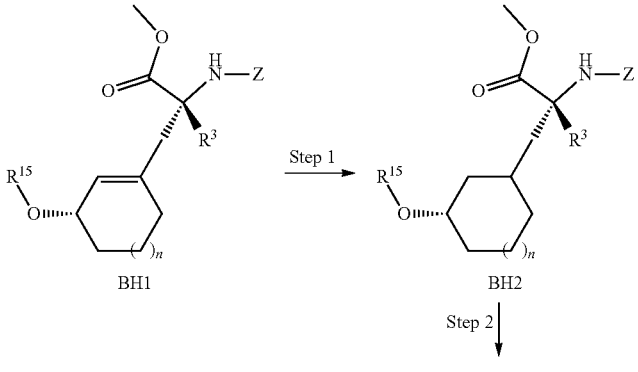
To a solution of BG1 (n=1, R^3=cyclohexylethyl) (0.136 g, 0.31 mmol) in CH_2Cl_2 was added 2,6-lutidine, AgOTf, and butyl iodide. The reaction was stirred at room temperature for 96 hours. The reaction was filtered through a pad of Celite, and the solution was concentrated. The residue was purified by silica chromatography (0-100% EtOAc/hexanes) to furnish BG2 (n=1, R^3=cyclohexylethyl, R^{15}=n-butyl) (0.124 g, 0.25 mmol, 80% yield). MS m/e: 426.1 (M-OBu).

The following compound was prepared using similar method:

BG3



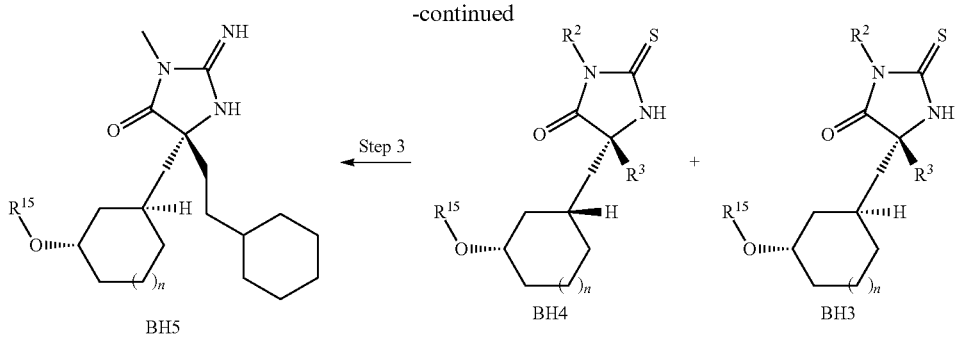
Method BH



BH1

BH2

-continued



Method BH, Step 1.

Compound BH1 (n=1, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.060 g, 0.12 mmol) and 5% $Pd(OH)_2/C$ (0.040 g) in EtOAc (1 mL)/MeOH (0.2 mL) was stirred under an atmosphere of H_2 for 20 hours at room temperature. The reaction was filtered through a pad of Celite, and the solution was concentrated. The crude product mixture BH2 (n=1, R^3=cyclohexylethyl and R^{15}=n-butyl) was carried on to the next step without purification.

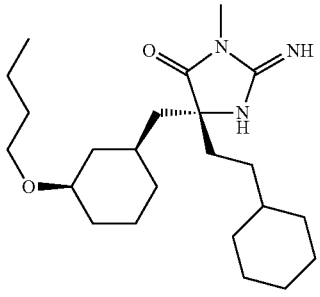
Method BH, Step 2.

A solution of BH2 (n=1, R^3=cyclohexylethyl and R^{15}=n-butyl) was converted to a product mixture of BH4 and BH3 using a method similar to Method C Step 1. The mixture was purified by silica gel chromatography using EtOAc/hexanes to yield BH4 (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.032 g, 0.078 mmol, 56% yield) and BH3 (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.008 g, 0.020 mmol, 14% yield). For BH4 (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl), MS m/e: 409.1 M+H). For BH3 (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl), MS m/e: 409.1 (M+H).

Method BH, Step 3.

Compound BH4 (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.032 g, 0.078 mmol) was converted to BH5 (n=1, R^2=Me, R^3=cyclohexylethyl and R^{15}=n-butyl) (0.016 g, 0.043 mmol, 57% yield) using a method similar to Method A, step 3. MS m/e: 392.1 (M+H).

The following compound was generated using a similar method:

#	Structure	MW	Obs. m/e
608		391	392

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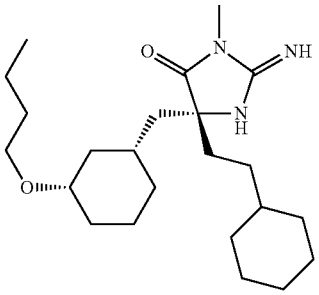
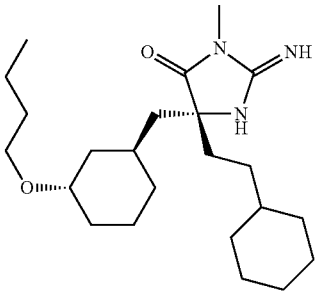
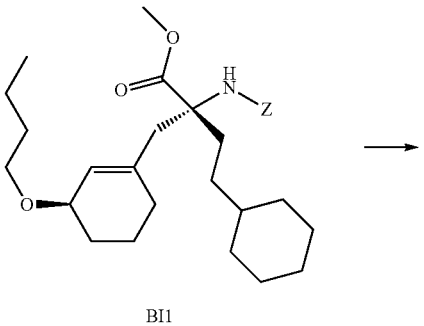
#	Structure	MW	Obs. m/e
609		391	392
610		391	392

Method BI



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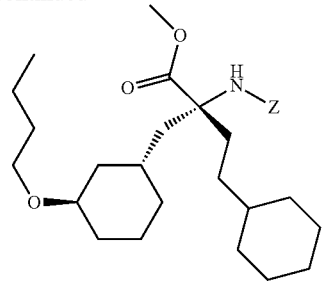
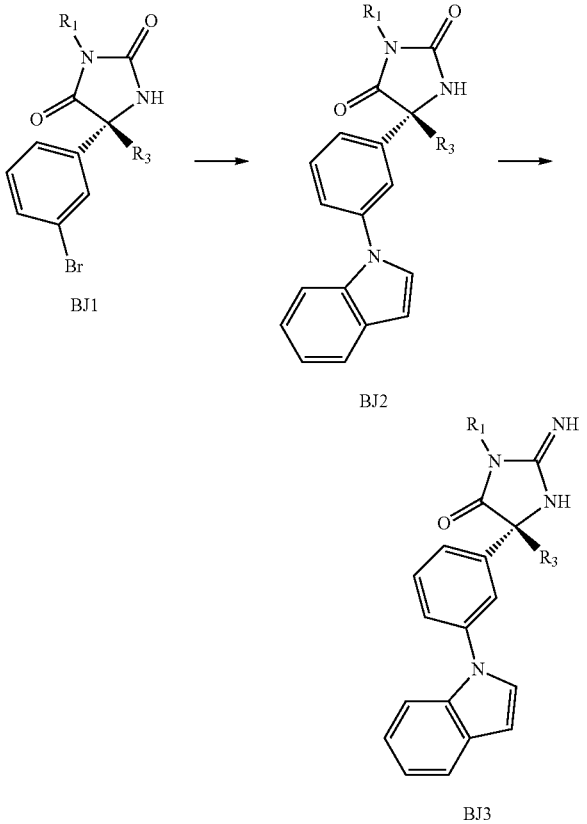


BI2

A solution of BI1(0.020 g, 0.040 mmol) in DCM (1 mL) was degassed using freeze/pump/thaw (4×) method. At the end of the fourth cycle Crabtree's catalyst was added and the system was evacuated. While thawing, the system was charged with hydrogen gas, and the reaction was stirred at room temperature for 16 hours under an H_2 atmosphere. The reaction was concentrated, and the brown oil was purified by reverse phase HPLC to furnish BI2(0.011 g, 0.022 mmol, 55% yield). MS m/e: 368.2 (M+H).

Method BJ



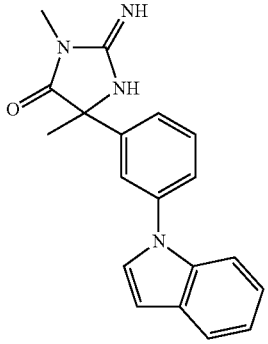
BJ1 BJ2 BJ3

Method BJ, Step 1

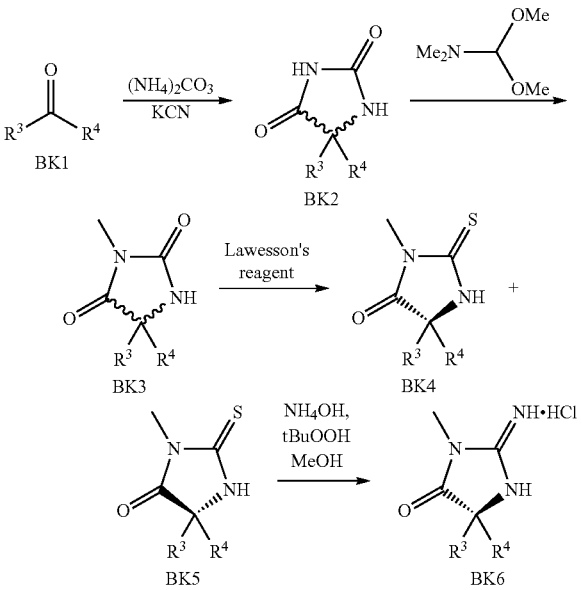
A mixture of 2 ml dioxane solution of BJ1 (R^1=Me, R^3=Me) (140 mg, 0.5 mmol) generated using Method BK Steps 1 & 2, indole (1.2 eq), potassium t-Butoxide (1.4 eq), $Pd_2(dba)_3$ (0.02 eq) and 2-di-t-butylphospinobiphenyl (0.04 eq) in a sealed tube was irradiated in a microwave oven at 120° C. for 10 min and the mixture was separated via a silica gel column to give BJ2(R^1=Me, R^3=Me) (0.73 mg).

Method BJ, Step 2

BJ2(R^1=Me, R^3=Me) was converted to BJ3 (R^1=Me, R^3=Me) using Method BK, Steps 3 & 4. Obs. Mass for BJ3 (R^1=Me, R^3=Me): 319.2.

#	Structure	MW	Obs. m/e
614		318	319

Method BK



BK1 BK2 BK3 BK4 BK5 BK6

Method BK, Step 1:

Hydantoin BK2 (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) was prepared according to Method D, Step 1 from the corresponding ketone BK1 (R^3=N-benzyl-3-piperidyl, R^4=n-Bu). Analytical data for BK2 (R^3=N-benzyl-3-piperidyl, R^4=n-Bu): (M+H)=330.1.

Method BK, Step 2:

To a suspension of hydantoin BK2 (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (138 mg, 0.419 mmol) in DMF (1.5 ml) was added dimethylformamide dimethylacetal (0.11 ml, 0.84

mmol). The resulting mixture was heated in a 100° C. oil bath for 16 h and then cooled to RT and concentrated under vacuum. This crude residue was purified by column chromatography (MeOH/DCM) to give product BK3 (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (140 mg, 0.408 mmol, 97%), (M+H)=344.1.

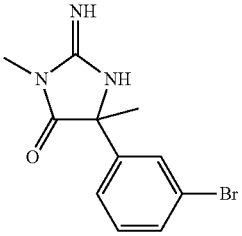
Method BK, Step 3:

To a solution of a portion of BK3 (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (70 mg, 0.20 mmol) in toluene (1 ml) was added Lawesson's reagent (107 mg, 0.26 mmol). The resulting mixture was placed in an oil bath at 60° C. for 16 h and then at 100° C. for 24 h. After cooling to RT, the reaction was quenched by addition of several drops of 1 N HCl and then diluted with EtOAc and 1 N KOH. The phases were separated and the aqueous layer extracted with EtOAc (2×). The organic portions were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. This crude residue was purified by preparative TLC (1000 μm silica, 15% EtOAc/DCM) to give two separated diastereomers BK4 (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (24 mg, 0.067 mmol, 33%, MS: (M+H)=360.2) and BK5 (R^3=N-benzyl-m-piperidyl, R^4=n-Bu) (22 mg, 0.062 mmol, 31%, MS: (M+H)=360.2).

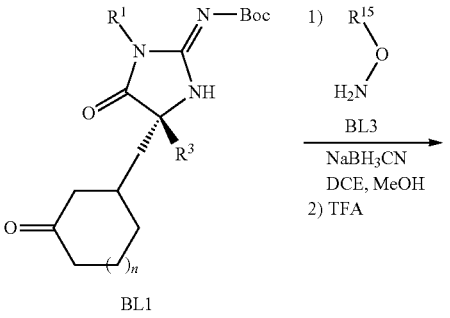
Method BK, Step 4:

Diastereomer BK5 (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) was treated with NH_4OH (2 ml) and t-butyl hydrogen peroxide (70% aqueous, 2 ml) in MeOH (4 ml) for 24 h. After concentration, the crude sample was purified by preparative TLC (1000 mm silica, 7.5% 7N NH_3/MeOH in DCM). The resulting sample was dissolved in DCM (1 ml), treated with 4N HCl in dioxane for 5 min, and finally concentrated to give diastereomeric products BK7 (R^3=N-benzyl-3-piperidyl, R^4=n-Bu) (12 mg, 0.029 mmol, 43%). ^{1}H NMR (CD_3OD) δ 7.60 (m, 2H), 7.49 (m, 3H), 4.39 (ABq, J_{AB}=12.8 Hz, $\Delta\nu_{AB}$=42.1 Hz, 2H), 3.69 (m, 1H), 3.39 (br d, J=13.6 Hz, 1H), 3.20 (s, 3H), 2.96 (m, 2H), 2.45 (m, 1H), 1.99 (m, 1H), 1.92-1.78 (m, 3H), 1.68 (br d, J=12.4 Hz, 1H), 1.50 (dq, J_d=3.6 Hz, J_q=12.8 Hz, 1H), 1.36-1.22 (m, 4H), 1.03 (m, 1H), 0.90 (t, J=7.2 Hz, 3H). LCMS: t_R (doubly protonated)=0.52 min, (singly protonated)=2.79 min; (M+H) for both peaks=343.2.

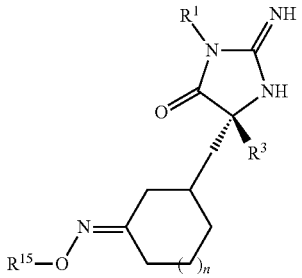
The following compounds were synthesized using similar methods:

#	Structure	MW	Obs. m/e
615		281	282

Method BL



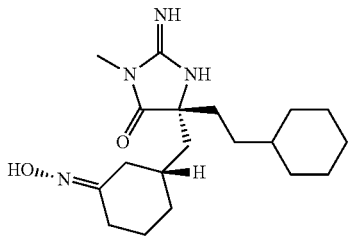
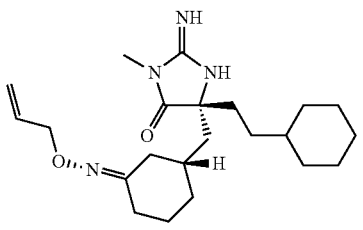
BL1



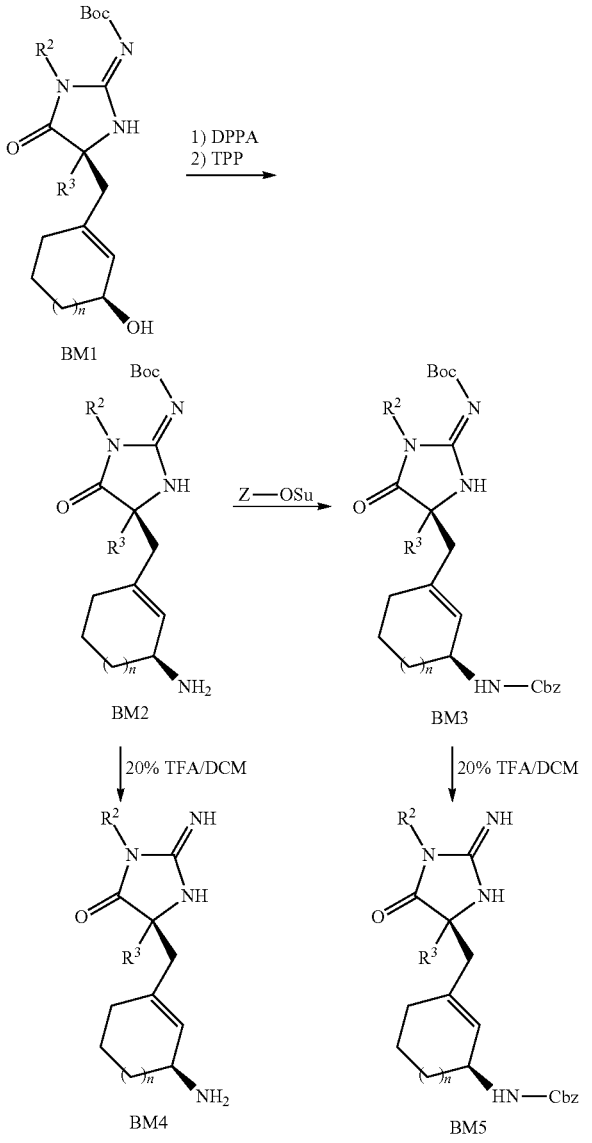
BL2

To a 2 ml Methanolic solution of BL1 (n=1, R^3=cyclohexylethyl, R^1=Me) (10 mg) was added BL3 (HCl salt, R^{15}=H, 2 eq) and NaOAc (2 eq) and the mixture was heated to 60 C for 16 h. After removal of solvent, the residue was treated with 20% TFA in DCM for 30 min before the solvent was evaporated and residue purified using a reverse phase HPLC to give BL2 (n=1, R^3=cyclohexylethyl, R^1=Me and R^{15}=H).

The following compounds were synthesized using similar methods.

#	Structure	MW	Obs. m/e
616		348	349
617		388	389

Method BM



Method BM, Step 1:

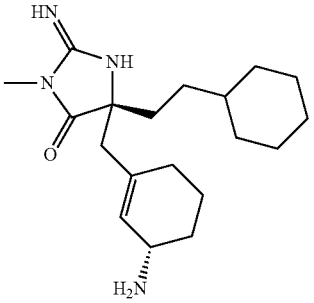
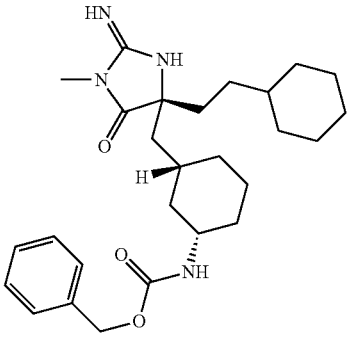
To a toulene solution (3 ml) of BM1 (n=1, R^3=cyclohexylethyl, R^2=Me) (0.050 mg) was added 1.5 eq of diphenylphosphorylazide and 1.5 eq of DBU and the solution was stirred at r.t. overnight. The reaction mixture was diluted with EtOAc and washed with 1% aq HOAc before the organic layer was dried and solvent evaporated. The residue was chromatographed using EtOAc/Hex to give a product that was treated with triphenylphosphine (2 eq) in THF (1% water) overnight to give BM2 (n=1, R^3=cyclohexylethyl, R^2=Me) after reverse phase purification.

Method BM Step 2:

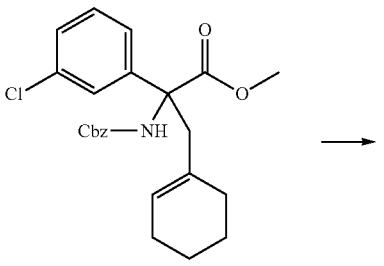
To a DCM solution of BM2 (n=1, R^3=cyclohexylethyl, R^2=Me) was added 1 eq of benzyloxycarbonyl-OSu and the reaction was stirred overnight before the solvent was evaporated and residue chromatographed to give BM3 (n=1, R^3=cyclohexylethyl, R^2=Me).

Compound BM4 (n=1, R^3=cyclohexylethyl, R^2=Me) and BM5 (n=1, R^3=cyclohexylethyl, R^2=Me) were generated from BM2 (n=1, R^3=cyclohexylethyl, R^2=Me) and BM3 (n=1, R^3=cyclohexylethyl, R^2=Me) through Boc-deprotection.

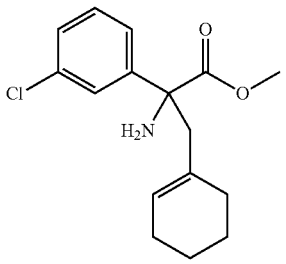
The following compounds were synthesized using similar method:

#	Structure	MW	Obs. m/e
618		332	333
619		468	469

Method BN



BN1

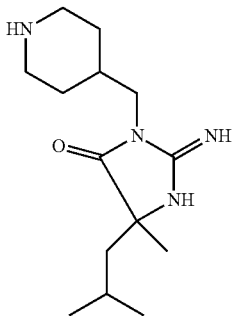
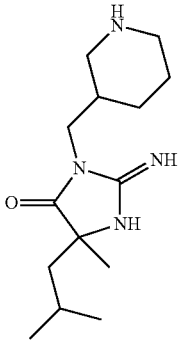
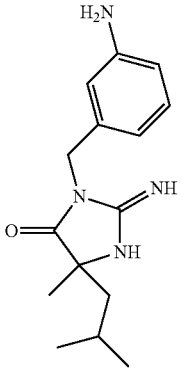
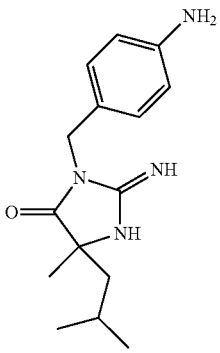


BN2

A mixture of $Pd(OAc)_2$ (9 mg), triethylamine (17 microliter), triethylsilane (11 microliter) and BN1 (20 mg) in DCM was hydrogenated at 1 atm at rt for 1.5 h before the reaction was filtered through a Celite pad to give BN2 after removal of solvent.

Method BO

The following compounds were generated through boc-deprotection of the corresponding starting material using 50% TFA in DCM, rt 30 min.

#	Structure	MW	Obs. m/e
620		266	267
621		266	267
622		274	275
623		274	275

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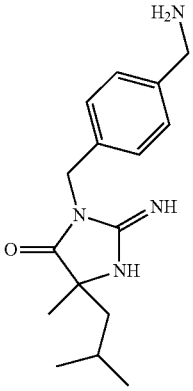
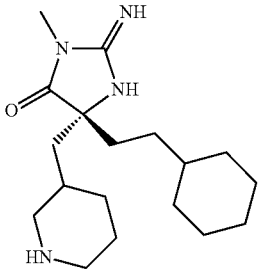
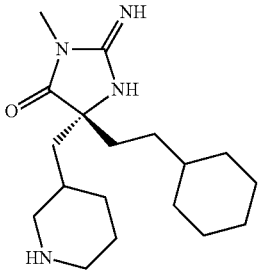
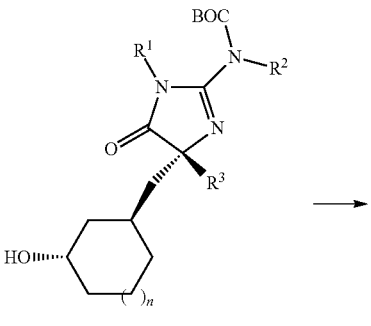
#	Structure	MW	Obs. m/e
624		288	289
625		320	321
626		320	321

Method BP



BP1

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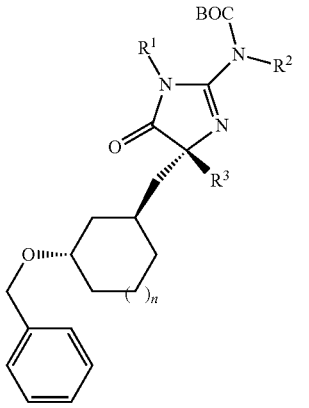
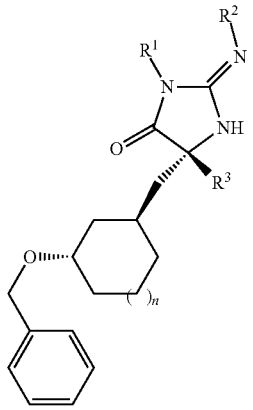


BP2



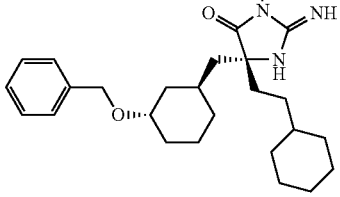
BP3

Method BP, Step 1

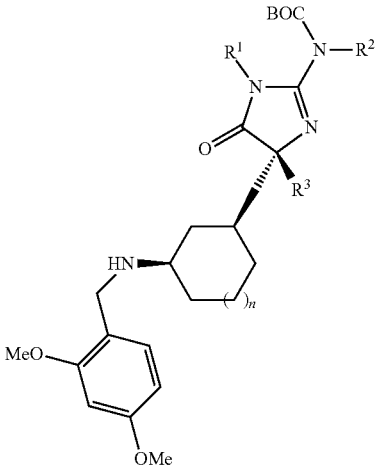
To a solution of BP1 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.012 g, 0.028 mmol) in CH_2Cl_2 (0.5 mL) was added 2,6-lutidine (0.010 mL, 0.086 mmol), AgOTf (0.024 g, 0.093 mmol), and benzyl bromide (0.010 mL, 0.084 mmol). The reaction was stirred at room temperature for 16 hours. The solid was filtered, and after concentration the residue was purified by reverse phase HPLC to yield BP2 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.010 g, 0.019 mmol). MS m/e: 526.1 (M+H).

Method BP, Step 2

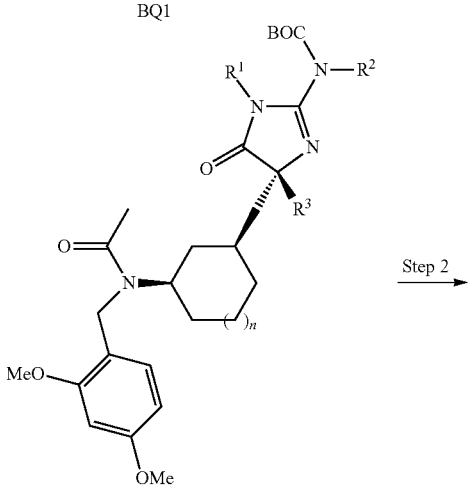
BP3 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) was prepared from BP2 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) using 30% TFA/DCM. MS m/e: 426.1 (M+H).

#	Structure	MW	Obs. m/e
627		425	426

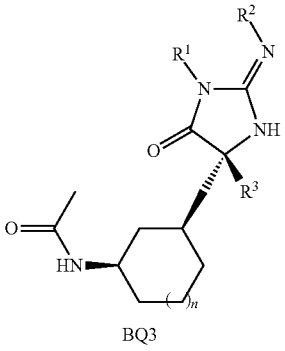
Method BQ



BQ1



BQ2



BQ3

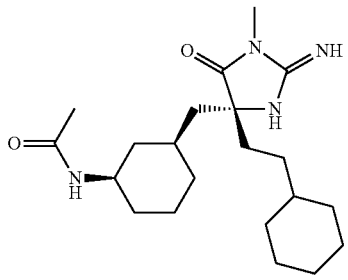
Method BQ Step 1:

BQ1 was prepared according to Method AZ.

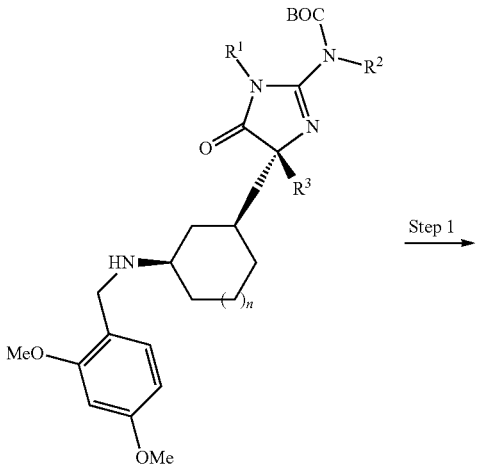
To a solution of BQ1 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.004 g, 0.007 mmol) in CH_2Cl_2 (0.3 mL) was added DIEA (0.007 mL, 0.040 mmol), acetic acid (0.001 mL, 0.017 mmol), HOBt (0.003 g, 0.019 mmol), and EDCI (0.003 g, 0.016 mmol). The reaction was stirred at room temperature for 16 hours. The reaction was concentrated and purified by reverse phase HPLC to provide BQ2 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.003 g, 0.005 mmol). MS m/e: 627.1 (M+H).

Method BQ Step 2:

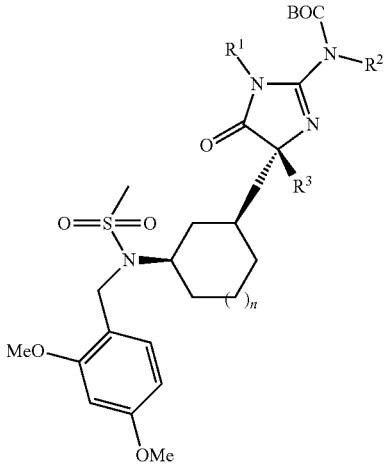
BQ2 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.003 g, 0.005 mmol) was treated with 20% TFA/CH_2Cl_2 (1 mL) in the presence of PS-thiophenol resin (0.030 g, 1.42 mmol/g) for 3 hours. The solution was filtered and concentrated to produce 603 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.002 g, 0.005 mmol). MS m/e: 377.2 (M+H).

#	Structure	MW	Obs. m/e
628		376	377

Method BR



BR1



BR2

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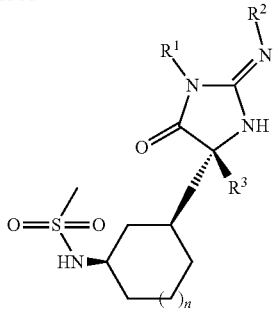


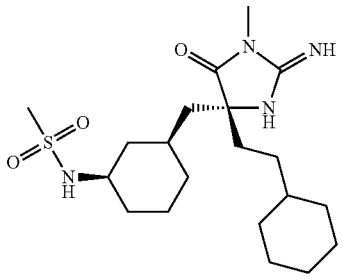
BR3

Method BR, Step 1:

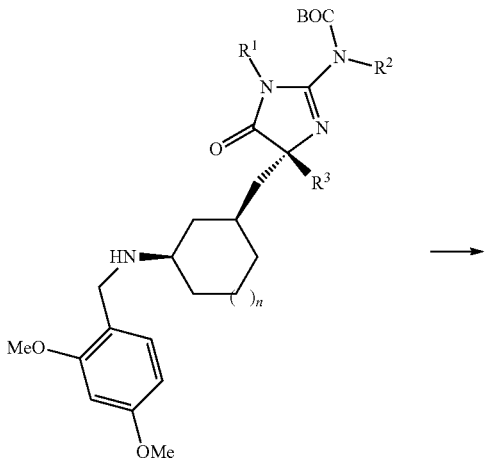
To a solution of BR^1 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.004 g, 0.007 mmol) in pyridine (0.2 ml) was added DMAP (a few crystals) and methylsulfonyl chloride (3 drops). The reaction was stirred at room temperature for 6 days. The reaction was quenched with water and diluted with CH_2Cl_2. The organic layer was removed, and the aqueous phase was extracted with CH_2Cl_2 (3×). After concentration, the brown residue was purified by reverse phase HPLC to yield BR^2 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.003 g, 0.004 mmol). MS m/e: 663.2 (M+H).

Method BR, Step 2:

BR^3 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) was prepared from BR^2 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) following a procedure similar to Method BQ Step 2. MS m/e: 413.1 (M+H).

#	Structure	MW	Obs. m/e
629		412	413

Method BS



BS1

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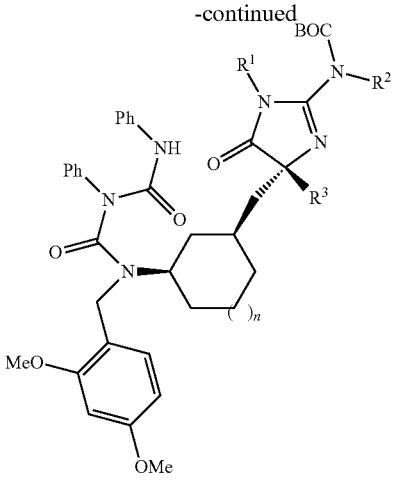
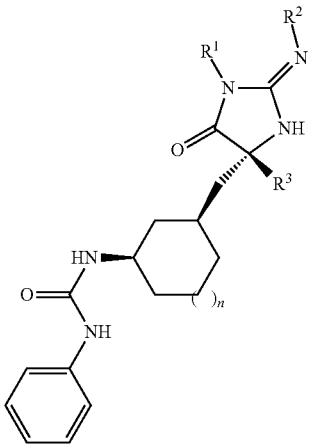


BS2



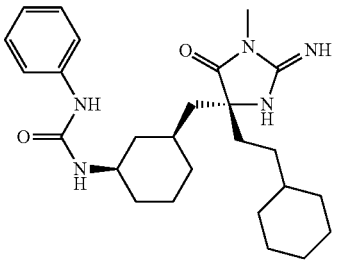
BS3

Method BS Step 1:

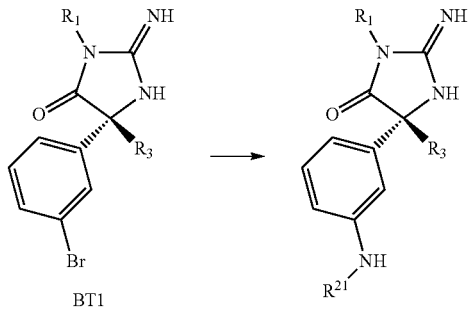
To a solution of BS1 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.003 g, 0.006 mmol) in CH_2Cl_2 (0.3 mL) was added phenyl isocyanate (2 drops). The reaction was stirred at room temperature for 16 hours. The reaction was concentrated and purified by reverse phase HPLC to provide BS2 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.002 g, 0.002 mmol). MS m/e: 823.5 (M+H).

Method BS Step 2:

Compound BS2 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) was subjected to the same conditions in Method BQ Step 2. The crude mixture prepared above was treated with LiOH (0.006 g, 0.25 mmol) in MeOH (0.3 mL) for 2 hours. The reaction was concentrated, and the residue was purified by reverse phase HPLC to furnish BS3 (n=1, R^1=Me, R^2=H, R^3=cyclohexylethyl) (0.0012 g, 0.002 mmol). MS m/e: 454.1 (M+H).

#	Structure	MW	Obs. m/e
630		453	454

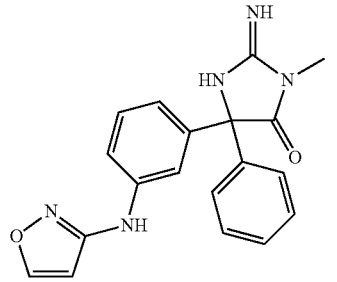
Method BT



BT1 BT2

Method BT:

To a round bottom flask were added compound BT1 (R^1=Me, R^3=Me) (100 mg, 0.29 mmol), anhydrous toluene (2 ml), 3-aminopyridine (55 mg, 0.58 mmol) and 2-(di-tert-butyl phosphino) biphenyl (17 mg, 0.058). The solution was then degassed by N_2 for 2 minutes before NaO-t-Bu (61 mg, 0.638 mmol) and $Pd_2(dba)_3$ (27 mg, 0.029 mmol) were added. The reaction was stirred at 80° C. for 22 hours. After cooling down to room temperature, the reaction was poured to cold water and extracted by CH_2Cl_2. The combined organic layer was then dried over Na_2SO_4. After the filtration, the concentrated residue was separated by TLC (CH_3OH:CH_2Cl_2=1:10) and reverse phase HPLC (10%-100% acetonitrile in water w/0.1% formic acid) to produce the desired compound BT2 (R^1=Me, R^3=Me and R^{21}=m-pyridyl) as a formate salt (23.6 mg, white solid, 20%). ^{1}HNMR ($CDCl_3$) δ 7.50-6.90 (m, 13H), 3.14 (s, 3H) MS m/e 358 (M+H).

#	Structure	MW	Obs. m/e
631		347	348

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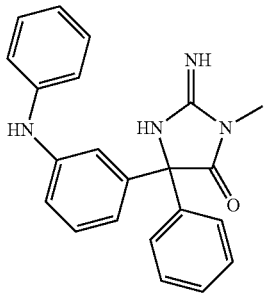
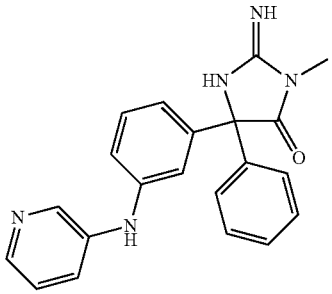
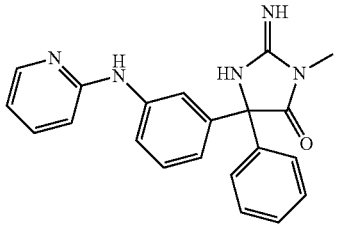
#	Structure	MW	Obs. m/e
632		156	357
633		357	358
634		357	358

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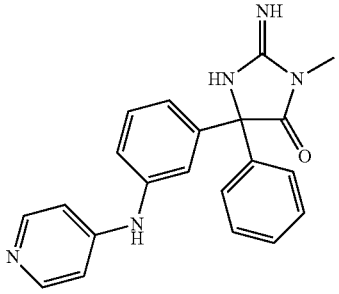
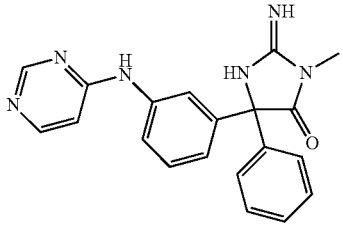
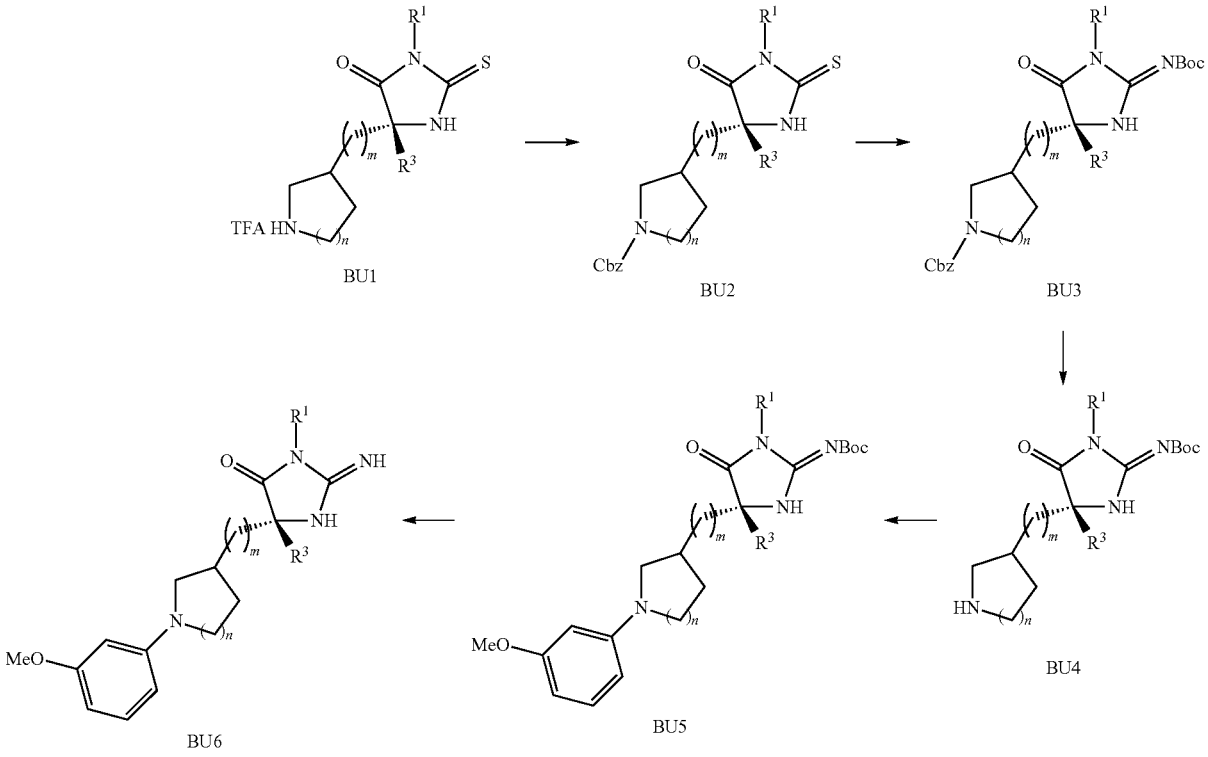
635		357	358
636		358	359

Method BU



Method BU, Step 1,

To a round bottomed flask containing BU1 (m=1, n=1, R^1=Me, R^3=Cyclohexylethyl) (99 mg, 0.307 mmol) of the trifluroacetic acid salt of pyrollidine derivative in 5 ml of DCM was added (86 μL, 0.614 mmol) of triethylamine followed by addition of (76 mg, 0.307 mmol) N-(benzyloxycarbonyloxy)succinimide. Stir at room temperature for 18 h. Dilute the mixture with DCM and extract with sat'd $NaHCO_3$ soln, then water. Collect the organic portion and dry over Na_2SO_4, filter and concentrate in vacuo. Purify by silica gel chromatography (eluting with 0 to 60% EtOAc/hexanes) to yield BU2 (m=1, n=1, R^1=Me, R^3=Cyclohexylethyl) (130 mg, 0.284 mmol, 93% yield). MS m/e: 458.1 (M+H).

Method BU, Step 2,

To a solution of BU2 (m=1, n=1, R^1=Me, R^3=Cyclohexylethyl) (130 mg) in 1 ml of MeOH in a reaction vial was added 0.5 ml of a solution of 70% tBuOOH in water and 0.5 ml of NH_4OH. Seal the vial and shake at room temperature for 72 h. The mixture was concentrated in vacuo. The mixture was diluted with 1 ml of MeOH and a mixture 30 mg of $NaHCO_3$ and Boc_2O (87 mg, 0.398 mmol) were added. The solution mixture was stirred at room temperature for 18 h before it was concentrated and the residue purified by silica gel chromatography using EtOAc/hexanes to yield the BU3 (m=1, n=1, R^1=Me, R^3=Cyclohexylethyl) (90 mg, 0.167 mmol, 58% yield). MS m/e: 541.1, 441.1 (M+H).

Method BU, Step 3,

A solution of BU3 (m=1, n=1, R^1=Me, R^3=Cyclohexylethyl) (90 mg, 0.167 mmol) in 5 ml of MeOH was hydrogenated using 100 mg of $Pd(OH)_2$—C (20% w/w) at 1 atm for 1 h. The reaction mixture was filtered through a pad of diatomaceous earth and the pad was washed with MeOH. Concentration of the collected organic portions in vacuo yielded BU4 (m=1, n=1, R^1=Me, R^3=Cyclohexylethyl) (47 mg 0.116 mmol, 70% yield). MS m/e: 407.1 (M+H).

Method BU, Step 4,

To a vial containing 10 mg of powdered 4 4' molecular sieves was added 3-methoxyphenyl boronic acid (60 mg, 0.395 mmol) then 3 ml of anhydrous MeOH. To this mixture was added pyridine (100 ml, 0.650 mmol), $Cu(OAc)_2$ (7 mg, 0.038 mmol), and BU4 (m=1, n=1, R^1=Me, R^3=Cyclohexylethyl) (7.83 mg, 0.019 mmol) and the mixture was stirred at room temperature for 96 h before it was quenched with 0.25 ml of 7N ammonia in methanol solution. The reaction mixture was extracted with water and DCM and the organic layers were dried and concentrate in vacuo. The residue was purified via a reverse-phase HPLC to give a product which was treated with 5 ml of 40% of TFA in DCM for 5 h. After removal of the volatiles, the residue was purified using a reverse phase HPLC system to furnish BU5 (m=1, n=1, R^1=Me, R^3=Cyclohexylethyl and R^{21}=m-MeOPh) as the formic acid salt (0.7 mg, 0.0015 mmol, 30.1% yield). MS m/e: 413.1 (M+H).

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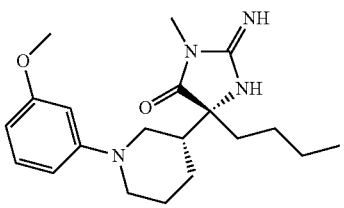
637		258	359

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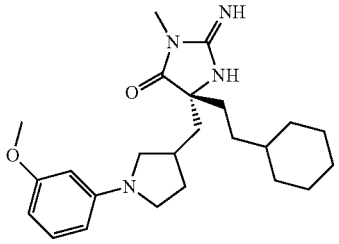
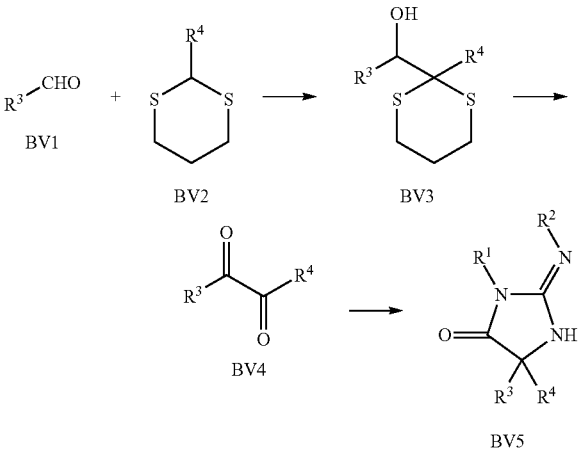
638		412	413

Method BV



Method BV Step 1:

The method was adapted from a literature procedure (Page et al., *Tetrahedron* 1992, 35, 7265-7274)

A hexane solution of nBuLi (4.4 mL, 11 mmol) was added to a −78 C solution of BV2 (R^4=phenyl) (2.0 g, 10 mmol) in THF (47 mL). After 60 minutes at −78 C, a solution of BV1 (R^3=3-bromo-4-fluorophenyl) (2.24 g, 11 mmol) was added and the reaction slowly warmed to RT over 18 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with CH_2Cl_2 (2×), dried over MgSO4 and concentrated under vacuum. The resulting oil was subjected to silica gel chromatography using 4-10% EtOAc/Hexanes to give a white solid BX3 (R^3=3-bromo-4-fluorophenyl and R^4=phenyl) (1.69 g, 4.23 mmol, 42%). ^{1}H NMR ($CDCl_3$) δ 7.61 (m, 2H), 7.27 (m, 3H), 6.94 (m, 1H), 6.92 (m, 1H), 6.68 (m, 1H), 3.15 (bs, 1H), 2.57-2.73 (m, 4H), 1.89 (m, 2H).

Method BV Step 2:

A solution of BV3 (R^3=3-bromo-4-fluorophenyl and R^4=phenyl) (1.69 g, 4.23 mmol) in acetone (40 mL) was slowly added via addition funnel to a 0° C. solution of N-bromosuccinimide (NBS, 11.3 g, 63.3 mmol) in acetone (200 mL) and water (7.5 mL). The mixture was slowly warmed to RT, and quenched after 60 minutes with 10% aqueous Na_2SO_3. After diluting with CH_2Cl_2, the layers were separated, and the organic layer washed with water (2×), brine (1×) and dried over $MgSO_4$. Concentration under vacuum afforded an oil which was subjected to silica gel chromatography using 5% EtOAc/Hexanes to give a solid BV4 (R^3=3-

bromo-4-fluorophenyl and R^4=phenyl) (690 mg, 2.24 mmol, 53%). ^1H NMR ($CDCl_3$) δ 8.19 (m, 1H), 7.93 (m, 3H), 7.66 (m, 1H), 7.50 (m, 2H), 7.20 (m, 1H).

Method BX Step 3:

BV5 (R^3=3-bromo-4-fluorophenyl and R^4=phenyl and R^1=Me and R^2=H) was prepared from BV4 (R^3=3-bromo-4-fluorophenyl and R^4=phenyl) using Method AS, Step 4.

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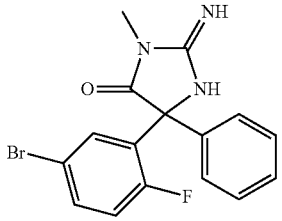
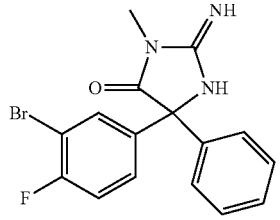
639		261	362
640		261	NA

Human Cathepsin D FRET Assay

This assay can be run in either continuous or endpoint format. Cathepsin D is an aspartic protease that possesses low primary sequence yet significant active site homology with the human aspartic protease BACE1. BACE1 is an amyloid lowering target for Alzheimer's disease. Cathespin D knock-out mice die within weeks after birth due to multiple GI, immune and CNS defects.

The substrate used below has been described (Y. Yasuda et al., J. Biochem., 125, 1137 (1999)). Substrate and enzyme are commercially available. A Km of 4 uM was determined in our lab for the substrate below under the assay conditions described and is consistent with Yasuda et al.

The assay is run in a 30 ul final volume using a 384 well Nunc black plate. 8 concentrations of compound are pre-incubated with enzyme for 30 mins at 37 C followed by addition of substrate with continued incubation at 37 C for 45 mins. The rate of increase in fluorescence is linear for over 1 h and is measured at the end of the incubation period using a Molecular Devices FLEX station plate reader. K is are interpolated from the IC50s using a Km value of 4 uM and the substrate concentration of 2.5 uM.

Reagents

Na-Acetate pH 5

1% Brij-35 from 10% stock (Calbiochem)

DMSO

Purified (>95%) human liver Cathepsin D (Athens Research & Technology Cat#16-12-030104)

Peptide substrate (Km=4 uM) Bachem Cat # M-2455

Pepstatin is used as a control inhibitor (Ki~0.5 nM) and is available from Sigma.

Nunc 384 well black plates

Final Assay Buffer Conditions

100 mM Na Acetate pH 5.0

0.02% Brij-35

1% DMSO

Compound is diluted to 3× final concentration in assay buffer containing 3% DMSO. 10 ul of compound is added to 10 ul of 2.25 nM enzyme (3×) diluted in assay buffer without DMSO, mixed briefly, spun, and incubated at 37 C for 30 mins. 3× substrate (7.5 uM) is prepared in 1× assay buffer without DMSO. 10 ul of substrate is added to each well mixed and spun briefly to initiate the reaction. Assay plates are incubated at 37 C for 45 mins and read on 384 compatible fluorescence plate reader using a 328 nm Ex and 393 nm Em.

Compounds of the present invention exhibit hCathD Ki data ranges from about 0.1 to about 500 nM, preferably about 0.1 to about 100 nM more preferably about 0.1 to about 75 nM.

The following are examples of compounds that exhibit hCathD Ki data under 75 nM.

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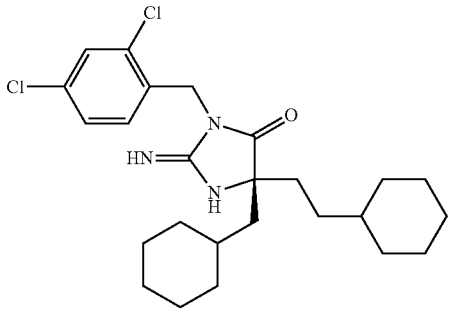
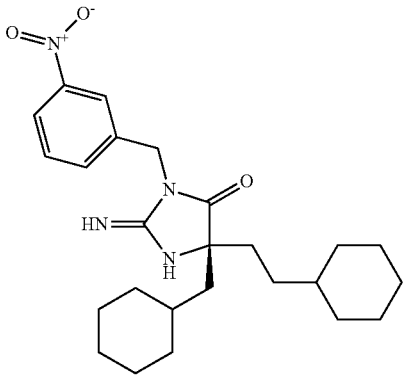
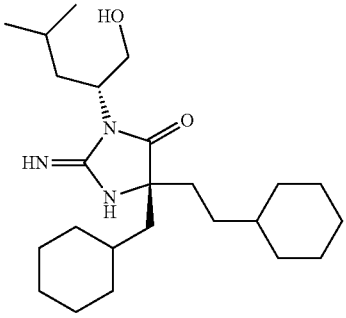

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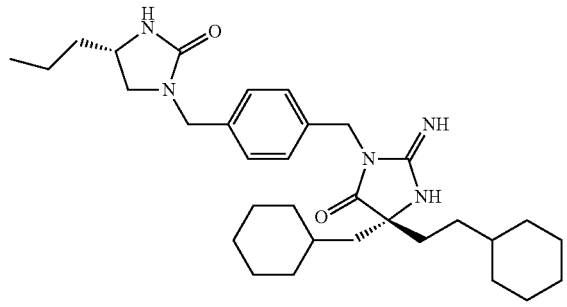
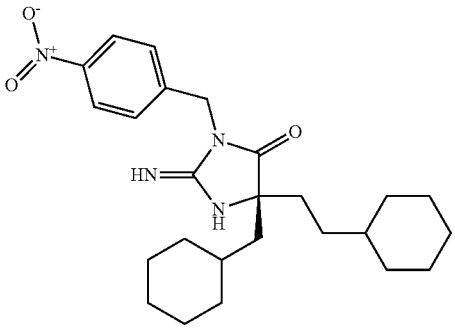
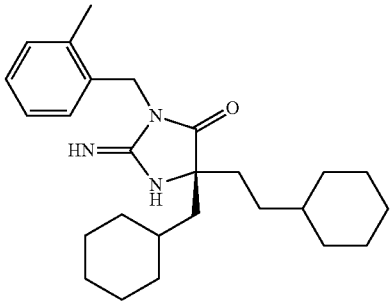
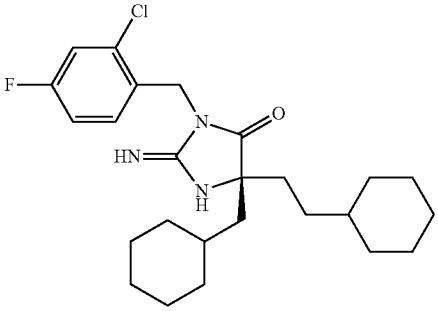

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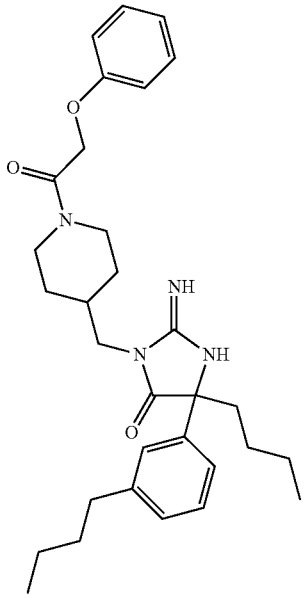
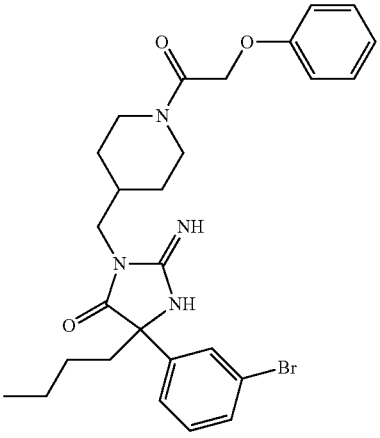
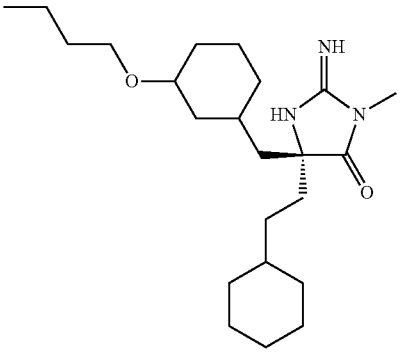

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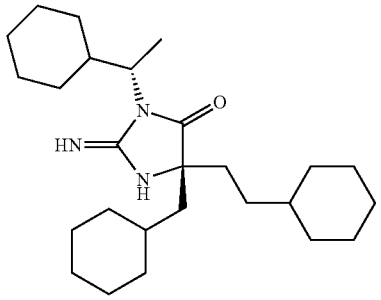
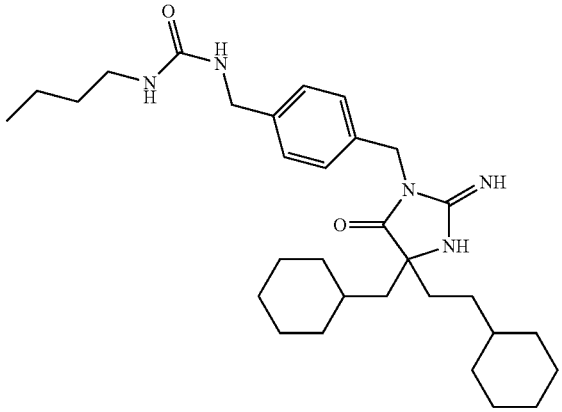
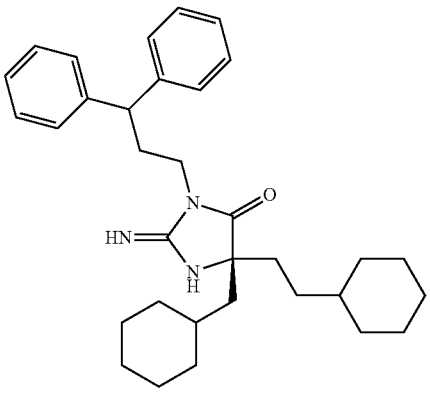

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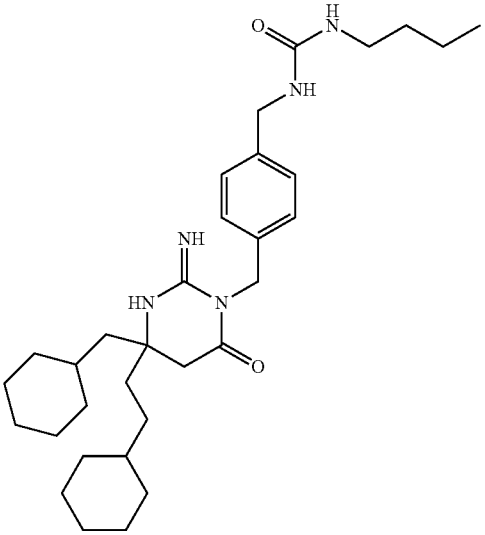
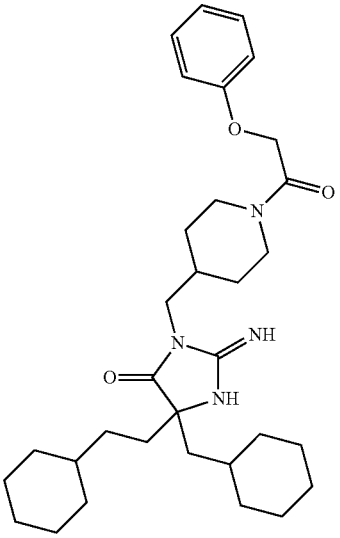
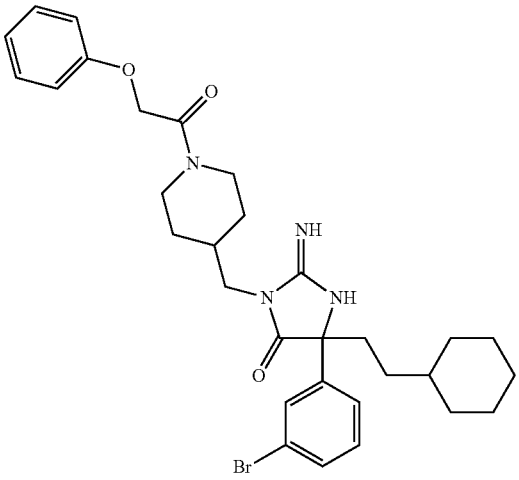

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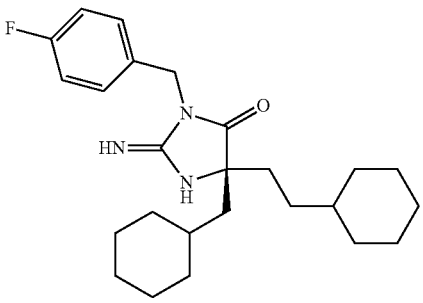
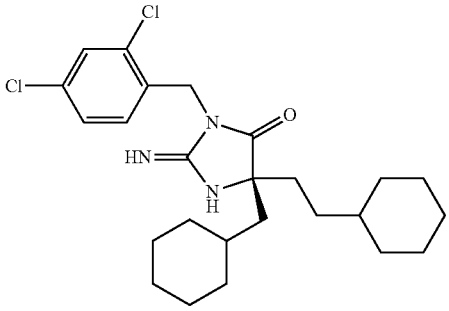


The following compound



has a hCath D Ki value of 0.45 nM.

BACE-1 Cloning, Protein Expression and Purification

A predicted soluble form of human BACE1 (sBACE1, corresponding to amino acids 1-454) was generated from the full length BACE1 cDNA (full length human BACE1 cDNA in pCDNA4/mycHisA construct; University of Toronto) by PCR using the advantage-GC cDNA PCR kit (Clontech, Palo Alto, Calif.). A HindIII/PmeI fragment from pCDNA4-sBACE1myc/His was blunt ended using Klenow and subcloned into the Stu I site of pFASTBACl(A) (Invitrogen). A sBACE1 mycHis recombinant bacmid was generated by transposition in DH10Bac cells (GIBCO/BRL). Subsequently, the sBACE1 mycHis bacmid construct was transfected into sf9 cells using CellFectin (Invitrogen, San Diego, Calif.) in order to generate recombinant baculovirus. Sf9 cells were grown in SF 900-II medium (Invitrogen) supplemented with 3% heat inactivated FBS and 0.5× penicillin/streptomycin solution (Invitrogen). Five milliliters of high titer plaque purified sBACEmyc/His virus was used to infect 1 L of logarithmically growing sf9 cells for 72 hours. Intact cells were pelleted by centrifugation at 3000×g for 15 minutes. The supernatant, containing secreted sBACE1, was collected and diluted 50% v/v with 100 mM HEPES, pH 8.0. The diluted medium was loaded onto a Q-sepharose column. The Q-sepharose column was washed with Buffer A (20 mM HEPES, pH 8.0, 50 mM NaCl).

Proteins, were eluted from the Q-sepharose column with Buffer B (20 mM HEPES, pH 8.0, 500 mM NaCl). The protein peaks from the Q-sepharose column were pooled and loaded onto a Ni-NTA agarose column. The Ni-NTA column was then washed with Buffer C (20 mM HEPES, pH 8.0, 500 mM NaCl). Bound proteins were then eluted with Buffer D (Buffer C, 250 mM imidazole). Peak protein fractions as determined by the Bradford Assay (Biorad, CA) were concentrated using a Centricon 30 concentrator (Millipore). sBACE1 purity was estimated to be ~90% as assessed by SDS-PAGE and Commassie Blue staining. N-terminal sequencing indicated that greater than 90% of the purified sBACE1 contained the prodomain; hence this protein is referred to as sproBACE1.

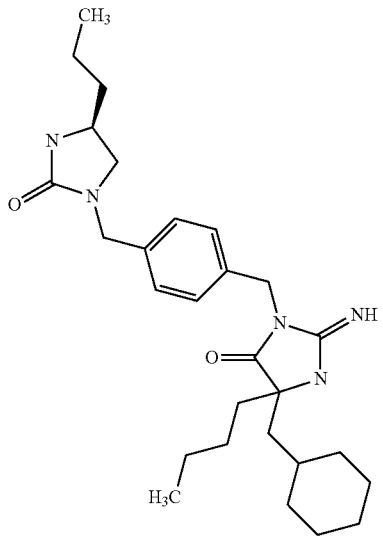
Peptide Hydrolysis Assay

The inhibitor, 25 nM EuK-biotin labeled APPsw substrate (EuK-KTEEISEVNLDAEFRHDKC-biotin (SEQ ID NO: 1); CIS-Bio International, France), 5 μM unlabeled APPsw peptide (KTEEISEVNLDAEFRHDK; (SEQ ID NO: 2) American Peptide Company, Sunnyvale, Calif.), 7 nM sproBACE1, 20 mM PIPES pH 5.0, 0.1% Brij-35 (protein grade, Calbiochem, San Diego, Calif.), and 10% glycerol were preincubated for 30 min at 30° C. Reactions were initiated by addition of substrate in a 5 μl aliquot resulting in a total volume of 25 μl. After 3 hr at 30° C. reactions were terminated by addition of an equal volume of 2x stop buffer containing 50 mM Tris-HCl pH 8.0, 0.5 M KF, 0.001% Brij-35, 20 μg/ml SA-XL665 (cross-linked allophycocyanin protein coupled to streptavidin; CIS-Bio International, France) (0.5 μg/well). Plates were shaken briefly and spun at 1200×g for 10 seconds to pellet all liquid to the bottom of the plate before the incubation. HTRF measurements were made on a Packard Discovery® HTRF plate reader using 337 nm laser light to excite the sample followed by a 50 μs delay and simultaneous measurements of both 620 nm and 665 nm emissions for 400 μs.

IC_{50} determinations for inhibitors, (I), were determined by measuring the percent change of the relative fluorescence at 665 nm divided by the relative fluorescence at 620 nm, (665/620 ratio), in the presence of varying concentrations of I and a fixed concentration of enzyme and substrate. Nonlinear regression analysis of this data was performed using GraphPad Prism 3.0 software selecting four parameter logistic equation, that allows for a variable slope. Y=Bottom+(Top−Bottom)/(1+10^((Log EC50−X)*HillSlope)); X is the logarithm of concentration of I, Y is the percent change in ratio and Y starts at bottom and goes to top with a sigmoid shape.

Compounds of the present invention have an IC_{50} range from about 0.1 to about 500 μM, preferably about 0.1 to about 100 μM, more preferably about 0.1 to about 20 μM. The last compound in Table M has an IC_{50} value of 0.35 μM.

Examples of compounds under 1 μM are listed below:



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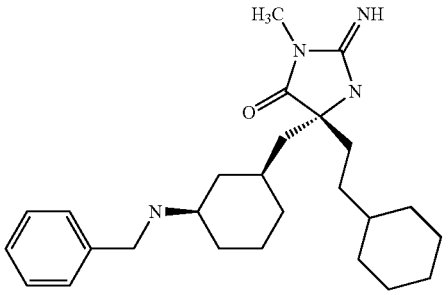

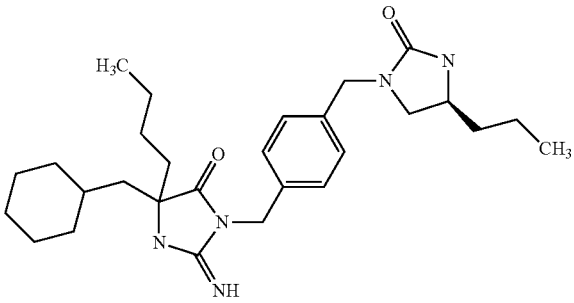

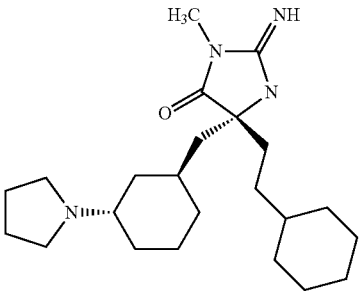

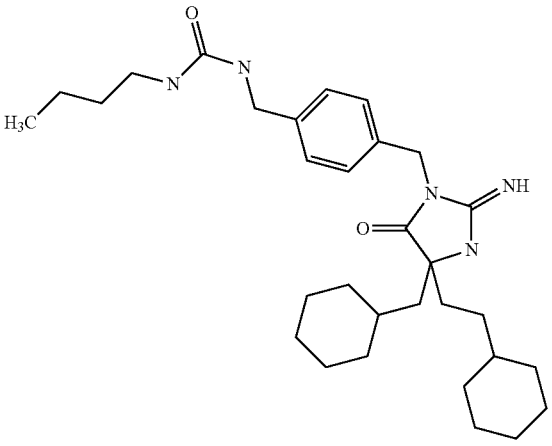

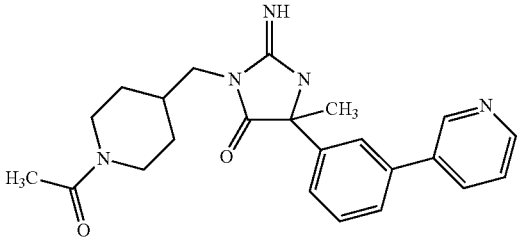

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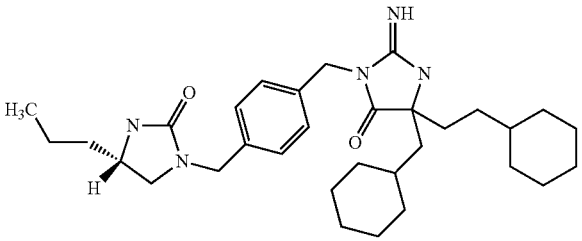

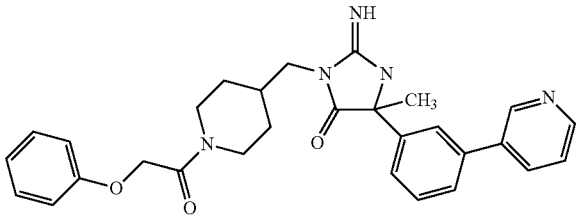

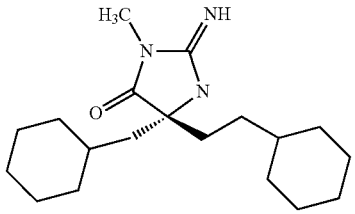

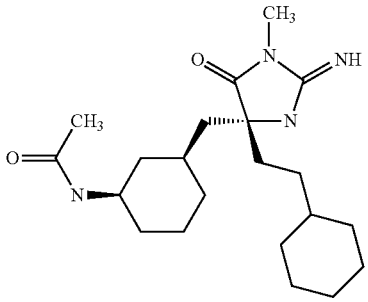

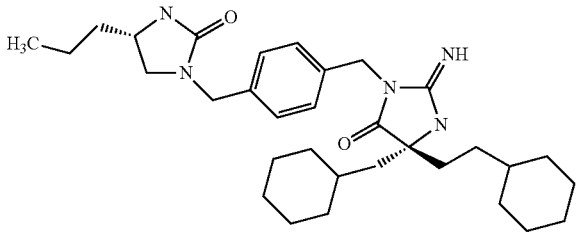

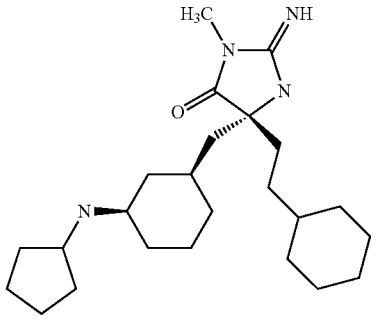

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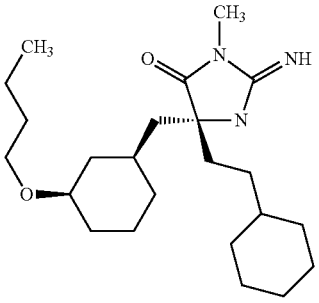

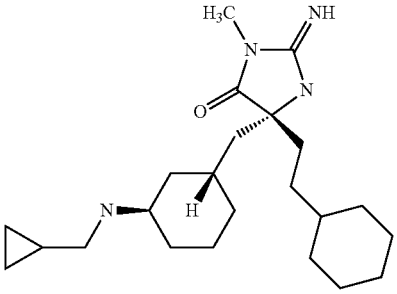

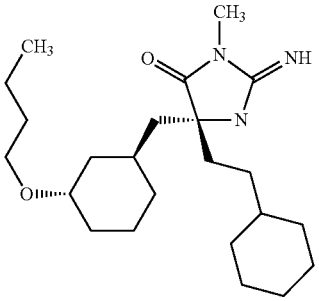

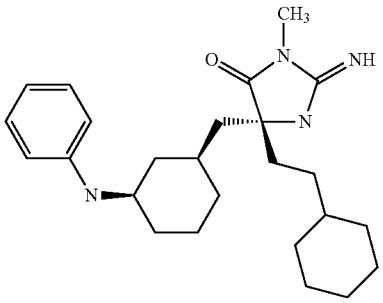

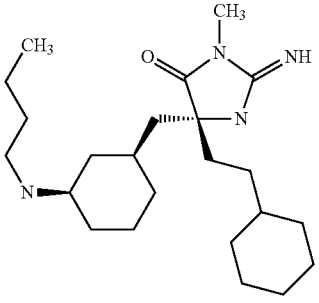

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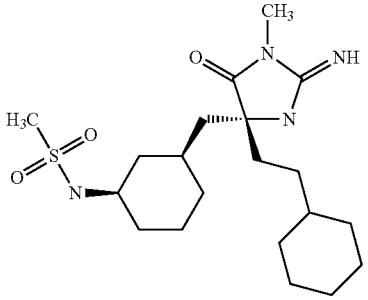

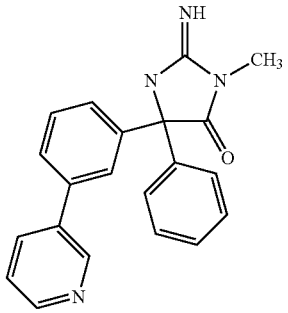

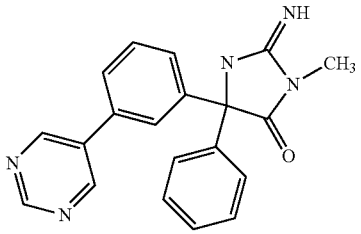

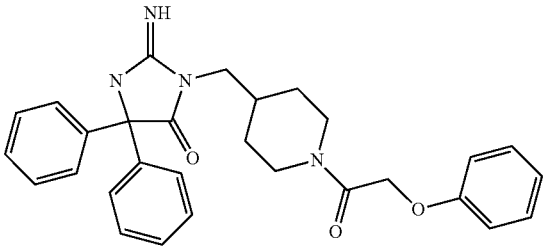

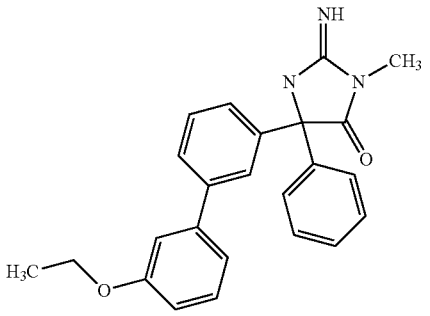

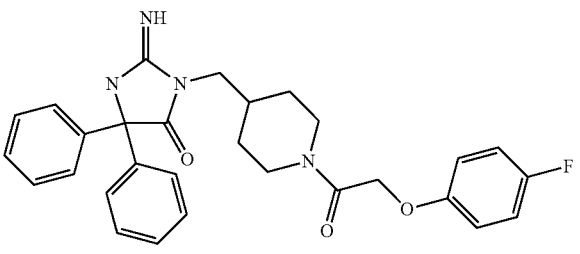

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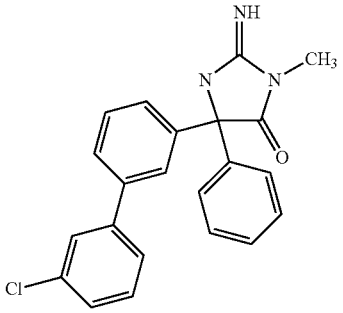

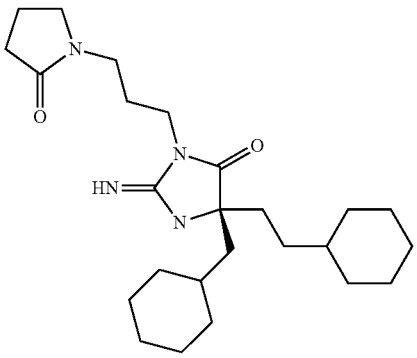

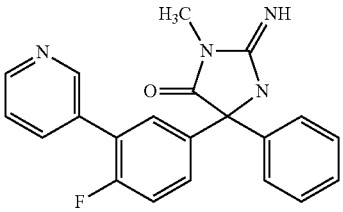

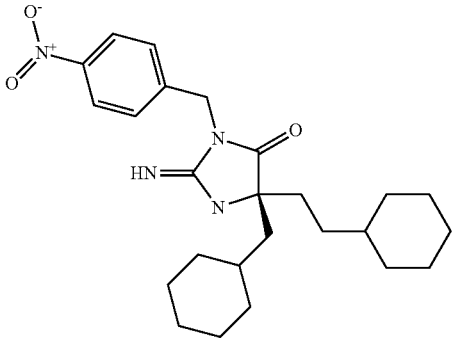

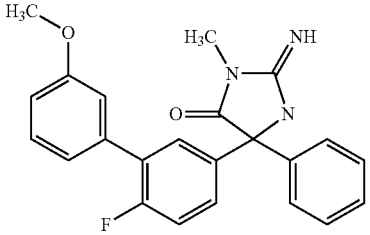

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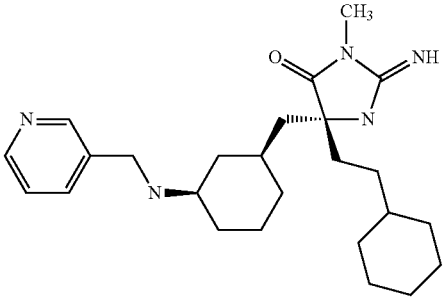

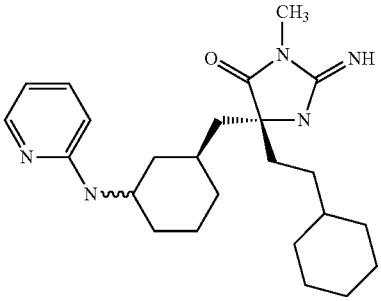

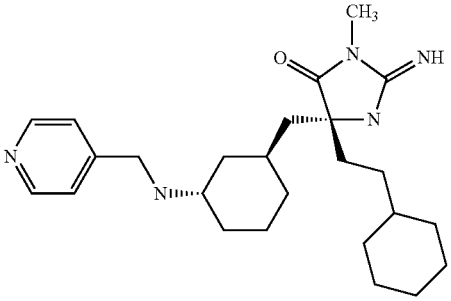

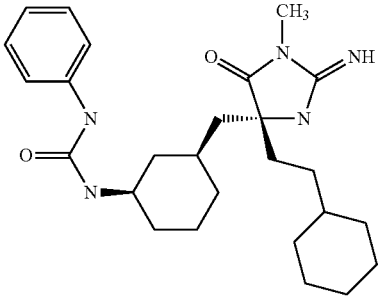

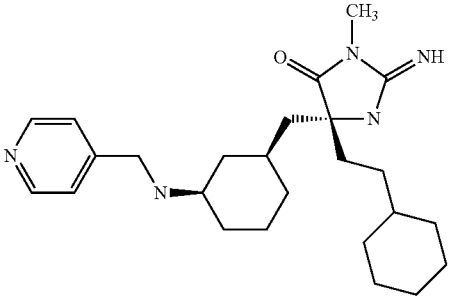

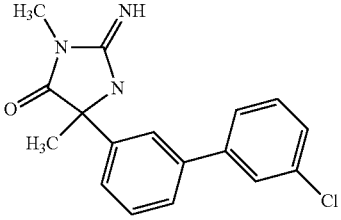

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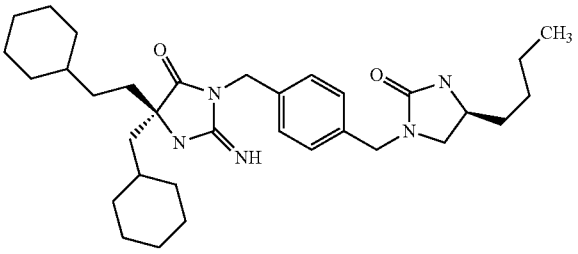

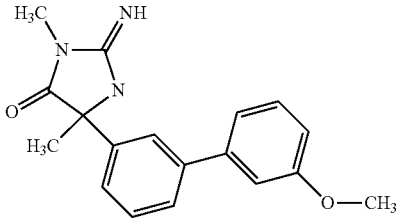

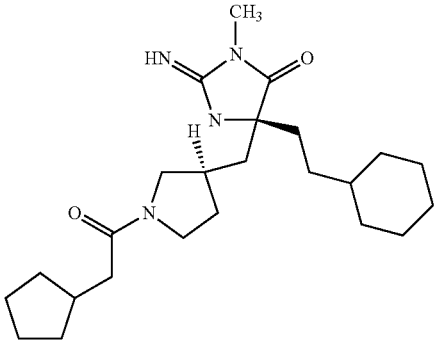

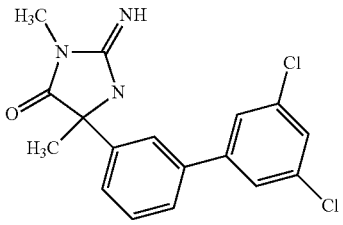

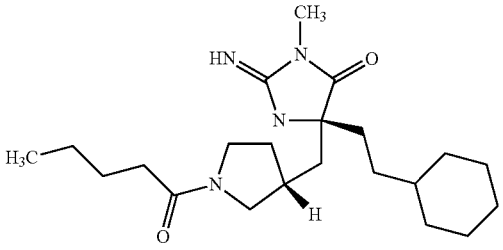

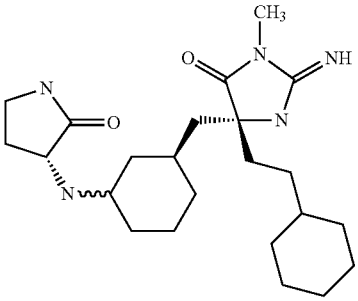

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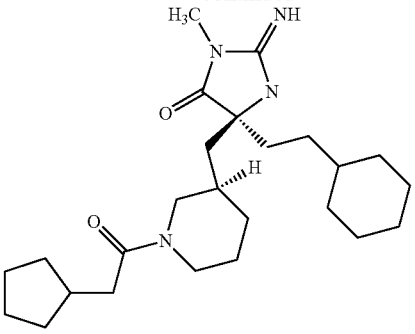

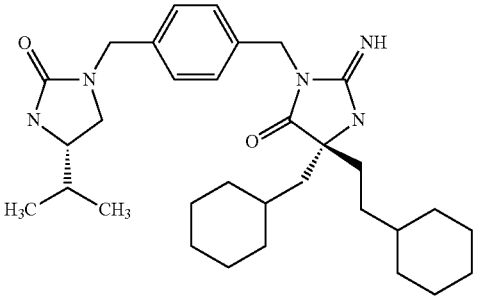

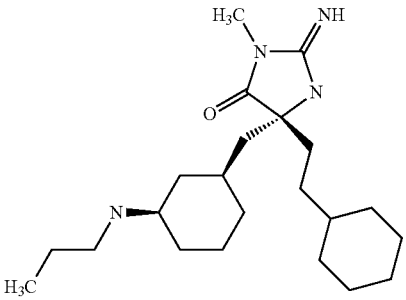

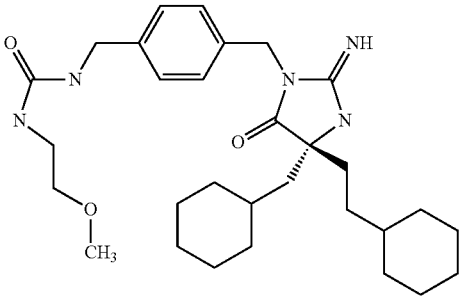

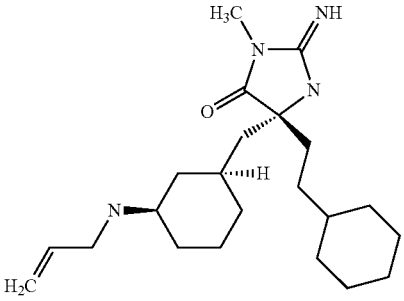

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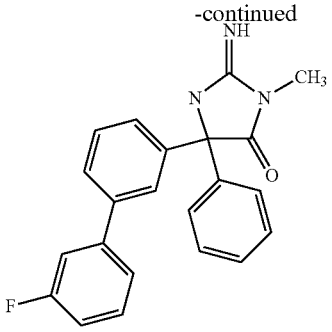
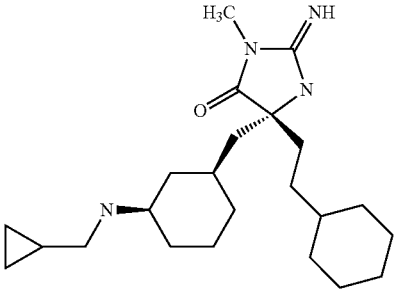
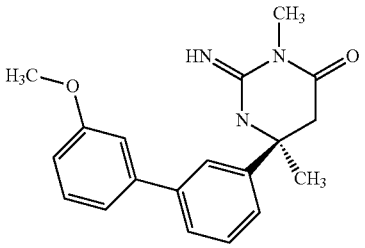
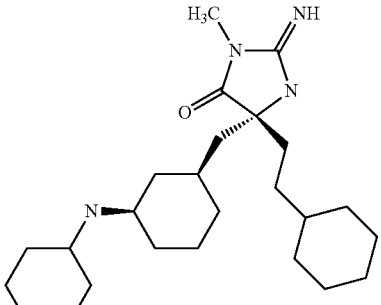
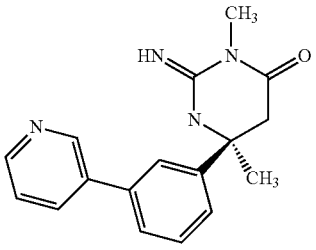




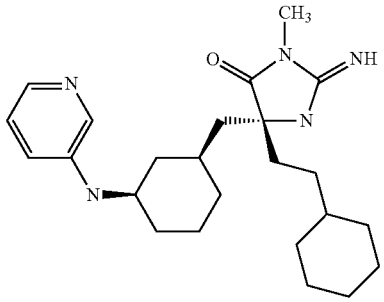
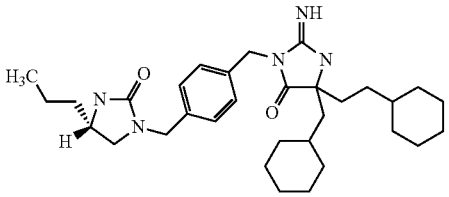
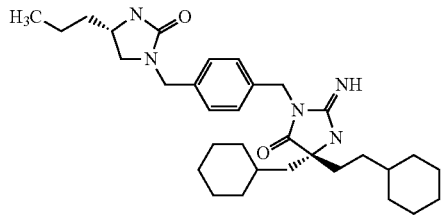






Human Mature Renin Enzyme Assay

Human Renin was cloned from a human kidney cDNA library and C-terminally epitope-tagged with the V5-6His sequence into pCDNA3.1. pCNDA3.1-Renin-V5-6His was stably expressed in HEK293 cells and purified to >80% using standard Ni-Affinity chromatography. The prodomain of the recombinant human renin-V5-6His was removed by limited proteolysis using immobilized TPCK-trypsin to give mature-human renin. Renin enzymatic activity was monitored using a commercially available fluorescence resonance energy transfer (FRET) peptide substrate, RS-1(Molecular Probes, Eugene, Oreg.) in 50 mM Tris-HCl pH 8.0, 100 mM NaCl, 0.1% Brij-35 and 5% DMSO buffer for 40 mins at 30 degrees celsius in the presence or absence of different concentrations of test compounds. Mature human Renin was present at approximately 200 nM. Inhibitory activity was defined as the percent decrease in renin induced fluorescence at the end of the 40 min incubation compared to vehicle controls and samples lacking enzyme.

Compound	1% of hRenin at 100 μM
	68.8
	75.3
	76.9

In the aspect of the invention relating to a combination of a compound of formula I with a cholinesterase inhibitor, acetyl- and/or butyrylcholinesterase inhibitors can be used. Examples of cholinesterase inhibitors are tacrine, donepezil, rivastigmine, galantamine, pyridostigmine and neostigmine, with tacrine, donepezil, rivastigmine and galaritamine being preferred.

In the aspect of the invention relating to a combination of a compound of formula I with a muscarinic antagonist, m_1 or m_2 antagonists can be used. Examples of m_1 antagonists are known in the art. Examples of m_2 antagonists are also known in the art; in particular, m_2 antagonists are disclosed in U.S. Pat. Nos. 5,883,096; 6,037,352; 5,889,006; 6,043,255; 5,952,349; 5,935,958; 6,066,636; 5,977,138; 6,294,554; 6,043,255; and 6,458,812; and in WO 03/031412, all of which are incorporated herein by reference.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or

lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pa.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 50 mg/day, in two to four divided doses.

When a compound of formula I is used in combination with a cholinesterase inhibitor to treat cognitive disorders, these two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a compound of formula I and a cholinesterase inhibitor in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional oral or parenteral dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the cholinesterase inhibitor can be determined from published material, and may range from 0.001 to 100 mg/kg body weight.

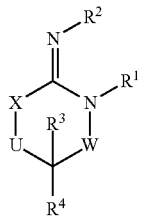
When separate pharmaceutical compositions of a compound of formula I and a cholinesterase inhibitor are to be administered, they can be provided in a kit comprising in a single package, one container comprising a compound of formula I in a pharmaceutically acceptable carrier, and a separate container comprising a cholinesterase inhibitor in a pharmaceutically acceptable carrier, with the compound of formula I and the cholinesterase inhibitor being present in amounts such that the combination is therapeutically effective. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

We claim:

1. A compound having the structural formula

I



or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

W is —O—;

X is —O—, —N(R^5)— or —C(R^6)(R^7)—; provided that when X is —O—, U is not —C(=O)— or —C(=NR^5)—;

U is —C(O)—, —P(O)(OR^{15})—, —C(=NR^5)—, or —(C(R^6)(R^7))$_b$—; wherein b is 1 or 2;

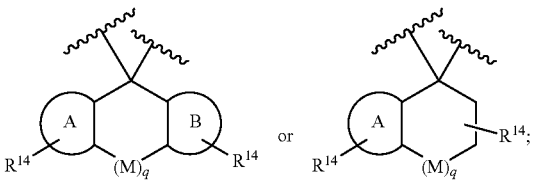
R^1 and R^5 are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, —OR^{15}—, —CN, —C(O)R^8, —C(O)OR^9, —S(O)R^{10}, —S(O)$_2$$R^{10}$, —C(O)N($R^{11}$)($R^{12}$), —S(O)N($R^{11}$)($R^{12}$), —S(O)$_2$N($R^{11}$)($R^{12}$), —$NO_2$, —N=C($R^8$)$_2$ and —N(R^8)$_2$, provided that R^1 and R^5 are not both selected from —NO_2, —N=C(R^8)$_2$ and —N(R^8)$_2$;

R^2 is H;

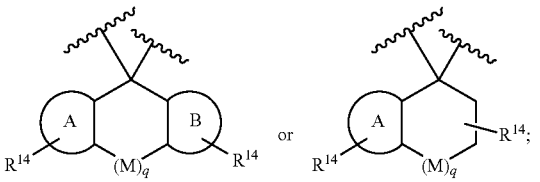
R^3, R^4, R^6 and R^7 are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CH_2—O—Si(R^9)(R^{10})(R^{19}), —SH, —CN, —OR^9, —C(O)R^8, —C(O)OR^9, —C(O)N(R^{11})(R^{12}), —SR^{19}, —S(O)N(R^{11})(R^{12}), —S(O)$_2$N(R^{11})(R^{12}), —N(R^{11})(R^{12}), —N(R^{11})C(O)R^8, —N(R^{11})S(O)R^{10}, —N(R^{11})C(O)N(R^{12})(R^{13}), —N(R^{11})C(O)OR^9 and —C(=NOH)R^8; provided that when U is —O— or —N(R^5)—, then R^3, R^4, R^6 and R^7 are not halo, —SH, —OR^9, —SR^{19}, —S(O)N(R^{11})(R^{12}), —S(O)$_2$N(R^{11})(R^{12}), —N(R^{11})(R^{12}), —N(R^{11})C(O)R^8, —N(R^{11})S(O)R^{10}, —N(R^{11})C(O)N(R^{12})(R^{13}), or —N(R^{11})C(O)OR^9; provided that R^3 and R^4 are not halo, —SH, —OR^9, —SR^{19}, —S(O)N(R^{11})(R^{12}), —S(O)$_2$N(R^{11})(R^{12}), —N(R^{11})(R^{12}), —N(R^{11})C(O)R^8, —N(R^{11})S(O)R^{10}, —N(R^{11})C(O)N(R^{12})(R^{13}), or —N(R^{11})C(O)OR^9;

or R^3, R^4, R^6 and R^7, together with the carbon to which they are attached, form a 3-7 membered cycloalkyl group optionally substituted by R^{14} or a 3-7 membered cycloalkylether optionally substituted by R^{14}

or R^3 and R^4 or R^6 and R^7 together with the carbon to which they are attached, are combined to form multicyclic groups such as



wherein M is —CH_2—, S, —$N(R^{19})$— or O, A and B are independently aryl or heteroaryl and q is 0, 1 or 2 provided that when q is 2, one M must be a carbon atom and when q is 2, M is optionally a double bond; and with the proviso that when R^3, R^4, R^6 and R^7 form said multicyclic groups



then adjacent R^3 and R^4 or R^6 and R^7 groups cannot be combined to form said multicyclic groups;

R^8 is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, —OR^{15}, —$N(R^{15})(R^{16})$, —$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$ and —$N(R^{15})C(O)OR^{16}$;

R^9 is independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

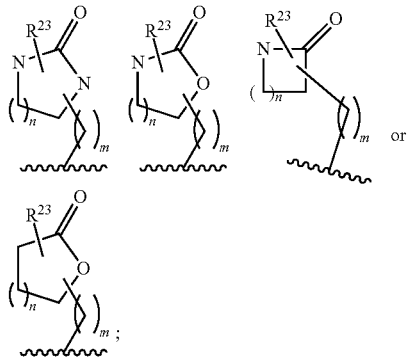
R^{10} is independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and —$N(R^{15})(R^{16})$;

R^{11}, R^{12} and R^{13} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^8$, —$C(O)OR^9$, —$S(O)R^{10}$, —$S(O)_2R^{10}$, —$C(O)N(R^{15})(R^{16})$, —$S(O)N(R^{15})(R^{16})$, —$S(O)_2N(R^{15})(R^{16})$ and —CN;

R^{14} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CN, —OR^{15}, —$C(O)R^{15}$, —$C(O)OR^{15}$, —$C(O)N(R^{15})(R^{16})$, —SR^{15}, —$S(O)N(R^{15})(R^{16})$, —$S(O)_2N(R^{15})(R^{16})$, —$C(=NOR^{15})R^{16}$, —$P(O)(OR^{15})(OR^{16})$, —$N(R^{15})(R^{16})$, —$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$ and —$N(R^{15})C(O)OR^{16}$;

R^{15}, R^{16} and R^{17} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, arylheterocycloalkyl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-cycloalkylalkyl, R^{18}-heterocycloalkyl, R^{18}-heterocycloalkylalkyl, R^{18}-aryl, R^{18}-arylalkyl, R^{18}-heteroaryl and R^{18}-heteroarylalkyl; or

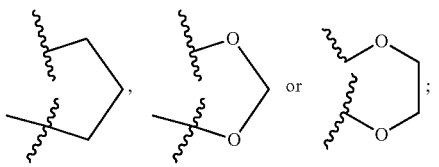
R^{15}, R^{16} and R^{17} are



wherein R^{23} numbers 0 to 5 substituents, m is 0 to 6 and n is 1 to 5;

R^{18} is 1-5 substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, —NO_2, halo, heteroaryl, HO-alkyoxyalkyl, —CF_3, —CN, alkyl-CN, —$C(O)R^{19}$, —C(O)OH, —$C(O)OR^{19}$, —$C(O)NHR^{20}$, —$C(O)NH_2$, —$C(O)NH_2$—$C(O)N(alkyl)_2$, —C(O)N(alkyl)(aryl), —C(O)N(alkyl)(heteroaryl), —SR^{19}, —$S(O)_2R^{20}$, —$S(O)NH_2$, —S(O)NH(alkyl), —S(O)N(alkyl)(alkyl), —S(O)NH(aryl), —$S(O)_2NH_2$, —$S(O)_2NHR^{19}$, —$S(O)_2NH$(heterocycloalkyl), —$S(O)_2N(alkyl)_2$, —$S(O)_2N$(alkyl)(aryl), —OCF_3, —OH, —OR^{20}, —O-heterocycloalkyl, —O-cycloalkylalkyl, —O-heterocycloalkylalkyl, —NH_2, —NHR^{20}, —$N(alkyl)_2$, —$N(arylalkyl)_2$, —N(arylalkyl)-(heteroarylalkyl), —$NHC(O)R^{20}$, —$NHC(O)NH_2$, —NHC(O)NH(alkyl), —NHC(O)N(alkyl)(alkyl), —N(alkyl)C(O)NH(alkyl), —N(alkyl)C(O)N(alkyl)(alkyl), —$NHS(O)_2R^{20}$, —$NHS(O)_2NH$(alkyl), —$NHS(O)_2N$(alkyl)(alkyl), —N(alkyl)$S(O)_2NH$(alkyl) and —N(alkyl)$S(O)_2N$(alkyl)(alkyl);

or two R^{18} moieties on adjacent carbons can be linked together to form



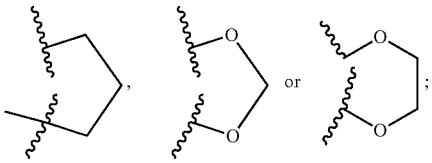
R^{19} is alkyl, cycloalkyl, aryl, arylalkyl or heteroarylalkyl;

R^{20} is alkyl, cycloalkyl, aryl, halo substituted aryl, arylalkyl, heteroaryl or heteroarylalkyl;

and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl,

heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently unsubstituted or substituted by 1 to 5 R^{21} groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CN, —OR^{15}, —$C(O)R^{15}$, —$C(O)OR^{15}$, —$C(O)N(R^{15})(R^{16})$, —SR^{15}, —$S(O)N(R^{15})(R^{16})$, —$CH(R^{15})(R^{16})$, —$S(O)_2N(R^{15})(R^{16})$, —$C(=NOR^{15})R^{16}$, —$P(O)(OR^{15})(OR^{16})$, —$N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, —$N(R^{15})C(O)R^{16}$, —CH_2—$N(R^{15})C(O)R^{16}$, —CH_2—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$CH_2$—$R^{15}$; —$CH_2N(R^{15})(R^{16})$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —$CH_2$—$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$, —$CH_2$—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)OR^{16}$, —$CH_2$—$N(R^{15})C(O)OR^{16}$, —$S(O)R^{15}$, $=NOR^{15}$, —N_3, —NO_2 and —$S(O)_2R^{15}$; and wherein each of the alkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{21} are independently unsubstituted or substituted by 1 to 5 R^{22} groups independently selected from the group consisting of alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, halo, —CF_3, —CN, —OR^{15}, —$C(O)R^{15}$, —$C(O)OR^{15}$, -alkyl-$C(O)OR^{15}$, $C(O)N(R^{15})(R^{16})$, —SR^{15}, —$S(O)N(R^{15})(R^{16})$, —$S(O)_2N(R^{15})(R^{16})$, —$C(=NOR^{15})R^{16}$, —$P(O)(OR^{15})(OR^{16})$, —$N(R^{15})(R^{16})$, -alkyl-$N(R^{15})(R^{16})$, —$N(R^{15})C(O)R^{16}$, —CH_2—$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —CH_2—$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$, —$CH_2$—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)OR^{16}$, —$CH_2$—$N(R^{15})C(O)OR^{16}$, —$N_3$, $=NOR^{15}$, —NO_2, —$S(O)R^{15}$ and —$S(O)_2R^{15}$;

or two R^{21} or two R^{22} moieties on adjacent carbons can be linked together to form



and when R^{21} or R^{22} are selected from the group consisting of —$C(=NOR^{15})R^{16}$, —$N(R^{15})C(O)R^{16}$, —CH_2—$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —CH_2—$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$, —$CH_2$—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)OR^{16}$ and —CH_2—$N(R^{15})C(O)OR^{16}$, R^{15} and R^{16} together can be a C_2 to C_4 chain wherein, optionally, one, two or three ring carbons can be replaced by —C(O)— or —N(H)— and R^{15} and R^{16}, together with the atoms to which they are attached, form a 5 to 7 membered ring, optionally substituted by R^{23};

R^{23} is 1 to 5 groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CN, —OR^{24}, —$C(O)R^{24}$, —$C(O)OR^{24}$, —$C(O)N(R^{24})(R^{25})$, —SR^{24}, —$S(O)N(R^{24})(R^{25})$, —$S(O)_2N(R^{24})(R^{25})$, —$C(=NOR^{24})R^{25}$, —$P(O)(OR^{24})(OR^{25})$, —$N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, —$N(R^{24})C(O)R^{25}$, —CH_2—$N(R^{24})C(O)R^{25}$, —$N(R^{24})S(O)R^{25}$, —$N(R^{24})S(O)_2R^{25}$, —CH_2—$N(R^{24})S(O)_2R^{25}$, —$N(R^{24})S(O)_2N(R^{25})(R^{26})$, —$N(R^{24})S(O)N(R^{25})(R^{26})$, —$N(R^{24})C(O)N(R^{25})(R^{26})$, —$CH_2$—$N(R^{24})C(O)N(R^{25})(R^{26})$, —$N(R^{24})C(O)OR^{25}$, —$CH_2$—$N(R^{24})C(O)OR^{25}$, —$S(O)R^{24}$ and —$S(O)_2R^{24}$; and wherein each of the alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkenyl and alkynyl groups in R^{23} are independently unsubstituted or substituted by 1 to 5 R^{27} groups independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, —CF_3, —CN, —OR^{24}, —$C(O)R^{24}$, —$C(O)OR^{24}$, alkyl-$C(O)OR^{24}$, $C(O)N(R^{24})(R^{25})$, —SR^{24}, —$S(O)N(R^{24})(R^{25})$, —$S(O)_2N(R^{24})(R^{25})$, —$C(=NOR^{24})R^{25}$, —$P(O)(OR^{24})(OR^{25})$, —$N(R^{24})(R^{25})$, -alkyl-$N(R^{24})(R^{25})$, —$N(R^{24})C(O)R^{25}$, —CH_2—$N(R^{24})C(O)R^{25}$, —$N(R^{24})S(O)R^{25}$, —$N(R^{24})S(O)_2R^{25}$, —CH_2—$N(R^{24})S(O)_2R^{25}$, —$N(R^{24})S(O)_2N(R^{25})(R^{26})$, —$N(R^{24})S(O)N(R^{25})(R^{26})$, —$N(R^{24})C(O)N(R^{25})(R^{26})$, —$CH_2$—$N(R^{24})C(O)N(R^{25})(R^{26})$, —$N(R^{24})C(O)OR^{25}$, —$CH_2$—$N(R^{24})C(O)OR^{25}$, —$S(O)R^{24}$ and —$S(O)_2R^{24}$;

R^{24}, R^{25} and R^{26} are independently selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, arylcycloalkyl, R^{27}-alkyl, R^{27}-cycloalkyl, R^{27}-cycloalkylalkyl, R^{27}-heterocycloalkyl, R^{27}-heterocycloalkylalkyl, R^{27}-aryl, R^{27}-arylalkyl, R^{27}-heteroaryl and R^{27}-heteroarylalkyl;

R^{27} is 1-5 substituents independently selected from the group consisting of alkyl, aryl, arylalkyl, —NO_2, halo, —CF_3, —CN, alkyl-CN, —$C(O)R^{28}$, —C(O)OH, —$C(O)OR^{28}$, —$C(O)NHR^{29}$, —$C(O)N(alkyl)_2$, —C(O)N(alkyl)(aryl), —C(O)N(alkyl)(heteroaryl), —SR^{28}, —$S(O)_2R^{29}$, —$S(O)NH_2$, —S(O)NH(alkyl), —S(O)N(alkyl)(alkyl), —S(O)NH(aryl), —$S(O)_2NH_2$, —$S(O)_2NHR^{28}$, —$S(O)_2NH$(aryl), —$S(O)_2NH$(heterocycloalkyl), —$S(O)_2N(alkyl)_2$, —$S(O)_2N$(alkyl)(aryl), —OH, —OR^{29}, —O-heterocycloalkyl, —O-cycloalkylalkyl, —O-heterocycloalkylalkyl, —NH_2, —NHR^{29}, —$N(alkyl)_2$, —$N(arylalkyl)_2$, —N(arylalkyl)(heteroarylalkyl), —$NHC(O)R^{29}$, —$NHC(O)NH_2$, —NHC(O)NH(alkyl), —NHC(O)N(alkyl)(alkyl), —N(alkyl)C(O)NH(alkyl), —N(alkyl)C(O)N(alkyl)(alkyl), —$NHS(O)_2R^{29}$, —$NHS(O)_2NH$(alkyl), —$NHS(O)_2N$(alkyl)(alkyl), —N(alkyl)$S(O)_2NH$(alkyl) and —N(alkyl)$S(O)_2N$(alkyl)(alkyl);

R^{28} is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl; and

R^{29} is alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

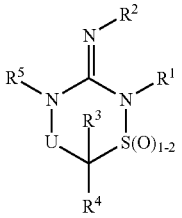
provided that neither R^1 nor R^5 is —C(O)-alkyl-azetidinone or alkyl di-substituted with (—$COOR^{15}$ or —$C(O)N(R^{15})(R^{16})$) and (—$N(R^{15})(R^{16})$, —$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —$N(R^{15})S(O)_2N(R^{16})(R^{17})$, —$N(R^{15})S(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$, or —$N(R^{15})C(O)OR^{16}$);

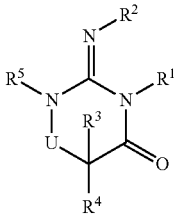
provided that when X is —$N(R^5)$—, U is —O— and W is —$C(R^6)(R^7)$—, (R^3,R^4) is not (H, —NHC(O)-alkyl-heteroaryl) or (H, alkyl-NHC(O)-alkyl-heteroaryl); and

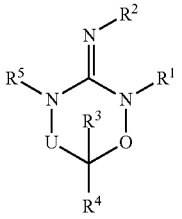
provided that when X is —$N(R^5)$—, R^1 and R^5 are not -alkylaryl-aryl-SO_2-$N(R^{15})(R^{16})$ wherein R^{15} is H and R^{16} is heteroaryl; and

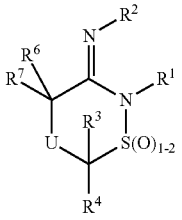
provided that when R^1 is R^{21}-aryl or R^{21}-arylalkyl, wherein R^{21} is —OCF_3, —$S(O)CF_3$, —$S(O)_2CF_3$, —S(O)alkyl, —$S(O)_2$alkyl, —$S(O)_2CHF_2$, —$S(O)_2CF_2CF_3$, —OCF^2CHF_2, —$OCHF_2$, —OCH_2CF_3, —SF_5 or —$S(O)_2NR^{15}R^{16}$; wherein R^{15} and R^{16} are independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, R^{18}-alkyl, R^{18}-cycloalkyl, R^{18}-heterocycloalkyl, R^{18}-aryl and R^{18}-heteroaryl; U is —CH_2; and X is —$N(R^5)$—; then R^5 is H.

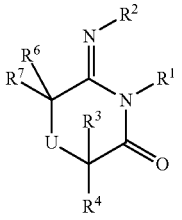
2. A compound of claim **1** having the structure

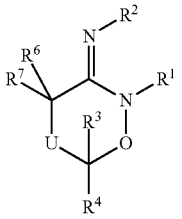
IA 

IB 

IC 

ID 

IE 

IF 

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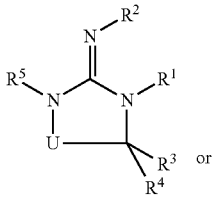
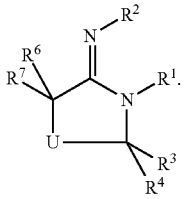
IG 

IH 

3. A compound of claim **2** wherein in structures IA to IF, U is —$C(R^6)(R^7)$—.

4. A compound of claim **2** of the structure IB wherein U is —$C(R^6)(R^7)$—.

5. A compound of claim **1** wherein R^3, R^4, R^6 and R^7 are independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, —CH_2—O—$Si(R^9)(R^{10})(R^{19})$, —SH, —CN, —OR^9, —$C(O)R^8$, —$C(O)OR^9$, —$C(O)N(R^{11})(R^{12})$, —SR^{19}, —$S(O)N(R^{11})(R^{12})$, —$S(O)_2N(R^{11})(R^{12})$, —$N(R^{11})(R^{12})$, —$N(R^{11})C(O)R^8$, —$N(R^{11})S(O)R^{10}$, —$N(R^{11})C(O)N(R^{12})(R^{13})$, —$N(R^{11})C(O)OR^9$ and —$C(=NOH)R^8$.

6. A compound of claim **1** wherein R^3, R^4, R^6 and R^7 are selected from the group consisting of aryl, heteroaryl, heteroarylalkyl, arylalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkyl and cycloalkylalkyl.

7. A compound of claim **1** wherein

U is —C(O)—;

W is —O—;

X is —$N(R^5)$—;

R^1 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkylalkyl or R^{21}-heterocycloalkylalkyl,

R^3 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

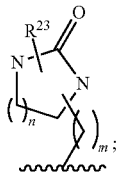
R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

R^5 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkylalkyl or R^{21}-heterocycloalkylalkyl;

R^6 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

R^7 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl or R^{21}-arylalkyl;

R^{15}, R^{16} and R^{17} is H, R^{18}-alkyl, alkyl or



R^{21} is alkyl, aryl, halo, —OR^{15}, —NO_2, —$C(O)R^{15}$, —CH_2—$N(R^{15})C(O)N(R^{16})(R^{17})$ or —$CH(R^{15})(R^{16})$;

n is 1;

m is 1;

R^{18} is —OR^{20}

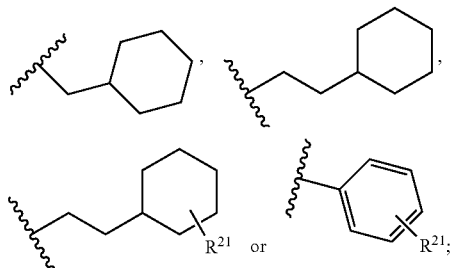
R^{20} is aryl;

and

R^{23} is alkyl.

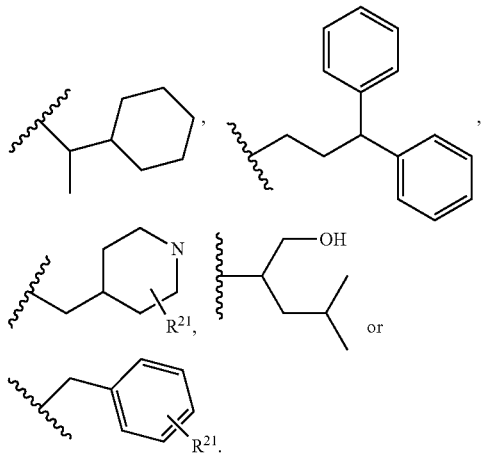
8. A compound of claim **7** wherein

R^3, R^4, R^6 and R^7 are



and

R^1 and R^5 is H, CH_3,



9. A compound of claim **1** wherein

U is —C(O)—;

W is —O—;

X is —$N(R^5)$—;

R^1 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkylalkyl or R^{21}-heterocycloalkylalkyl,

R^3 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

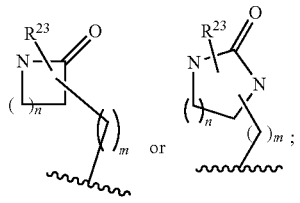
R^4 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^5 is H, alkyl, R^{21}-alkyl, arylalkyl, R^{21}-arylalkyl, cycloalkylalkyl, R^{21}-cycloalkylalkyl, heterocycloalkylalkyl or R^{21}-heterocycloalkylalkyl;

R^6 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^7 is alkyl, cycloalkylalkyl, cycloalkyl, aryl, arylalkyl, R^{21}-alkyl, R^{21}-cycloalkylalkyl, R^{21}-cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, heteroarylalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl, R^{21}-heteroarylalkyl, R^{21}-heteroaryl, R^{21}-heterocycloalkyl or R^{21}-heterocycloalkylalkyl;

R^{15}, R^{16} and R^{17} is H, cycloalkyl, cycloalkylalkyl, R^{18}-alkyl, alkyl, aryl, R^{18}-aryl, R^{18}-arylalkyl, arylalkyl,



n is 1 or 2;

m is 0 or 1;

R^{18} is —OR^{20} or halo;

R^{20} is aryl or halo substituted aryl;

R^{21} is alkyl, aryl, heteroaryl, R^{22}-alkyl, R^{22}-aryl, R^{22}-heteroaryl, halo, heterocycloalkyl, —$N(R^{15})(R^{16})$, —OR^{15}, —NO_2, —$C(O)R^{15}$, —$N(R^{15})C(O)R^{16}$, —$N(R^{15})S(O)_2R^{16}$, —CH_2—$N(R^{15})C(O)N(R^{16})(R^{17})$, —$N(R^{15})C(O)N(R^{16})(R^{17})$ or —$CH(R^{15})(R^{16})$;

R^{22} is —OR^{15} or halo

and

R^{23} is H or alkyl.

10. A pharmaceutical composition comprising an effective amount of a compound of claim **1** and a pharmaceutically effective carrier.

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